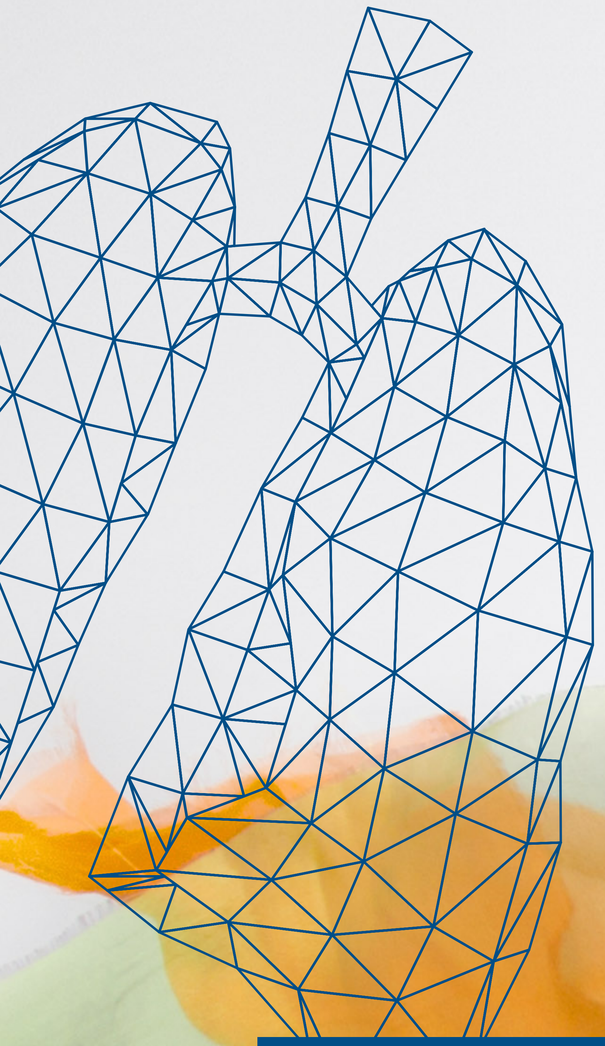
FROM RECOGNISING ALPHA-1 TO **HELPING YOUR PATIENTS MANAGE THE CONDITION**



Your patient may suffer from alpha-1 antitrypsin deficiency. As it is a rare disease, patients understandably have many questions and concerns. This guide will help you to better understand all the disease-related aspects to be able to support them through their journey.

There is also a matching patient guide that will help explain these concepts to the patient in an easy-to-understand way.

GRIFOLS

ALPHA$_1$-ANTITRYPSIN DEFICIENCY

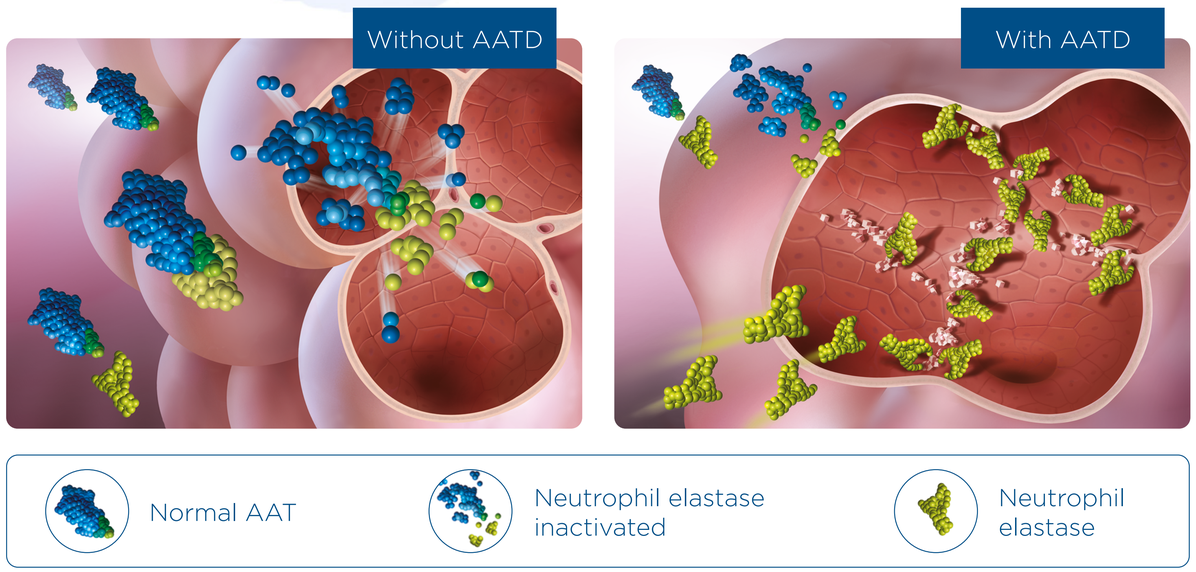
- Alpha$_1$-antitrypsin deficiency (AATD) is a genetic disorder characterised by the deficit or absence of liver-produced **alpha$_1$ antitrypsin (AAT)** in the blood, which can lead to **chronic obstructive pulmonary disease (COPD)** and chronic liver disease.[1,2]
- The most reported symptoms in AATD patients include dyspnea, wheezing and cough and conditions such as, early-onset emphysema and bronchiectasis.[3] This is why it is **often diagnosed and treated as COPD or asthma** after a pulmonary function test.[3]

WHY IS ALPHA-1 OFTEN UNDERDIAGNOSED?

- As a **rare disease**, AATD is often **underdiagnosed** due to poor awareness and its variable clinical presentation consistent with other more common diseases such as COPD and chronic liver disease.[4-6]
- Some of the clinical syndromes associated with AATD include **COPD, bronchitis** (excessive cough and sputum production) and **emphysema** (chronic dyspnea with lung tissue destruction).[7]
- Despite smoking being the main risk factor for COPD, it is estimated that **1–3% of COPD/emphysema patients have AATD.**[1,7] These patients are largely undetected and vulnerable to a more rapid loss of lung function.[3]

HOW DOES AATD CAUSE LUNG AND LIVER DISEASE?

- The AAT protein is a protease inhibitor encoded by the ***SERPINA1* gene** and synthesised mainly in the **liver**.[3,4,8]
- ATT protects the alveolar matrix from **neutrophil elastase*** proteolytic attack in episodes of inflammation by infection or inhaled irritants (tobacco).[3,4,8]
- Mutations in AAT cause deficiencies in the protein secretion and lead to their **accumulation** within the hepatocytes, **damaging lung tissue**.[8]
- The secretory defect and accumulation issues are associated with **a low AAT level**, exposing the lung tissue to proteolytic attacks from neutrophil elastase leading to **alveolar destruction** and panacinar emphysema.[8]
- AATD is also associated with premature onset of **COPD**, **liver cirrhosis**, and other **inflammatory autoimmune** and **neoplastic** diseases.[1] It also confers a **greater risk** of serious liver diseases such as **hepatitis C infection** and **cystic fibrosis**.[3]



*Neutrophil elastase is responsible for the host defence mechanism to withstand infections and minimise their impact.[9]

WHAT IS THE USUAL SYMPTOMATOLOGY?

- Due to the similarity to other liver and lung diseases such as COPD, **more than 90% of AATD patients remain incorrectly diagnosed**.[10]
- Early diagnosis is crucial to slow the degeneration. Some of the symptoms or diseases associated with AATD are:[11]

Lungs	Liver
COPD	Neonatal cholestasis (jaundice, with hyperbilirubinaemia and raised serum aminotransferase levels)
Emphysema	Extrahepatic biliary atresia
Chronic bronchitis	Gestational alloimmune liver disease (neonatal haemochromatosis)
Bronchiectasis	Chronic viral hepatitis
Granulomatosis with polyangiitis (GPA)	Alcoholic and non-alcoholic steatohepatitis
Obstructive lung disease	Sclerosing cholangitis
Asthma	Primary biliary cholangitis
Dyspnea	Panniculitus
Cough	Liver cirrhosis (children)
Wheezing	Liver abnormalities (children)
Sputum production (phlegm)	Portal hypertension (children)
Decreased expiratory airflow	Liver cirrhosis and fibrosis
Increased lung volumes	Hepatocellular carcinoma
Decreased diffusing capacity	Liver inclusions

WHAT ARE THE GENE VARIANTS INVOLVED?

The *SERPINA1* gene is pleomorphic, with more than 150 allelic variants of AAT identified; however, not all of them cause pathology. There are mainly two **deficiency variants**, **S** and **Z**.[12-14]

The three main known alpha-1 alleles are classified as:[14]

- The **healthy allele**, referred to as the **"M"**, most people have two copies of this allele (MM) per cell (homozygous).
- The **deficiency allele**, referred to as the **"S"**, producing moderate levels of AAT (SS).
- The **deficiency allele**, referred to as the **"Z"** allele, causing severe protein deficiency (ZZ).
- **Null allele**, no detectable protein synthesis.

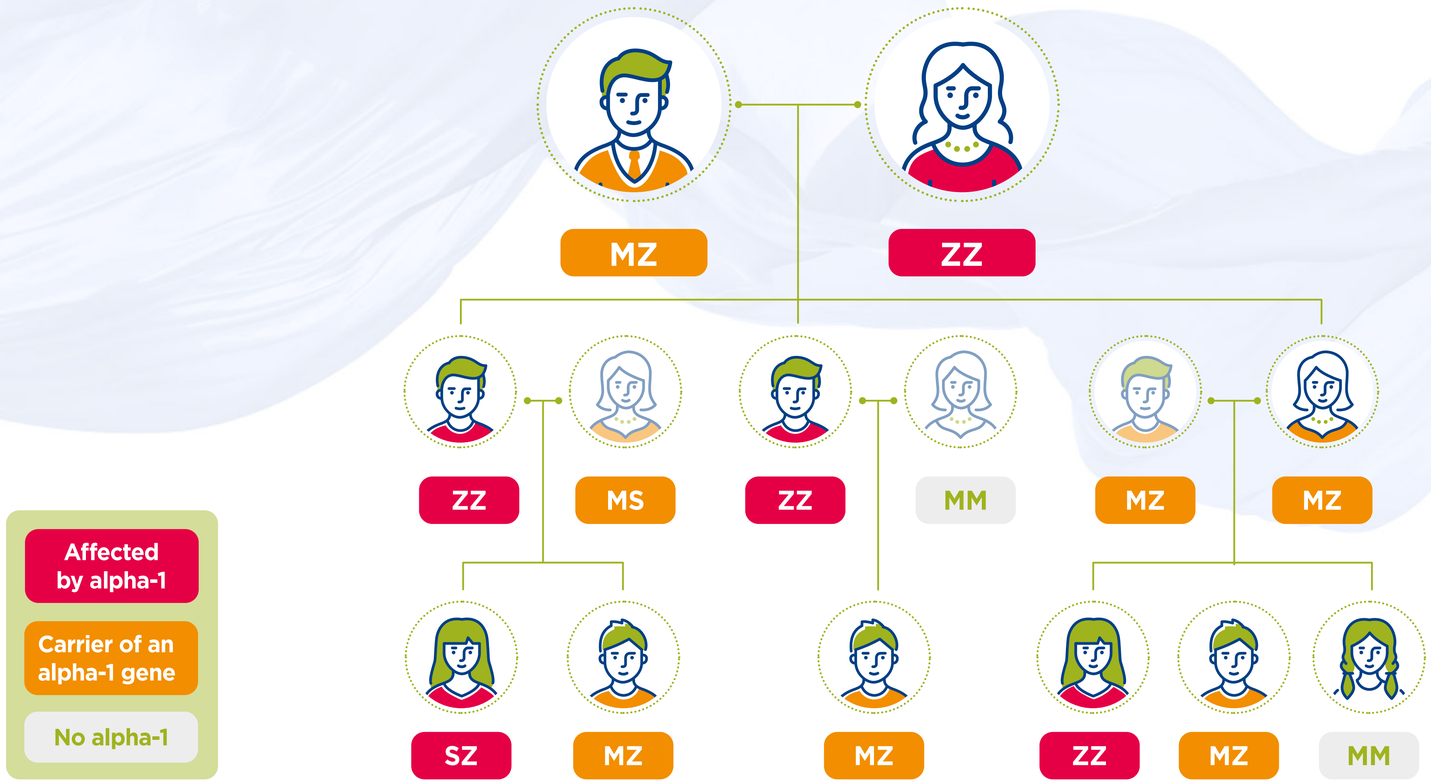
The combination of different alleles can lead to different pathologies.[13-15] See the main combinations here.

WHAT ARE THE GENE VARIANTS INVOLVED?

Allele combination	Patient description	AAT levels	Risk of lung and/or liver disease
MM	Normal	33 (20-53) µmol/L	-
MS	Carrier	33 (18-52) µmol/L	Patients with an abnormal AAT gene. Most studies do not show an increased risk of disease. It is unclear whether there is a risk of getting disease symptons.
MZ	Carrier	25.4 (15-42) µmol/L	**Mild to moderate AAT Deficiency** — patients carrying an abnormal AAT gene. They may get disease symptoms.
SS	Alpha-1	28 (20-48) µmol/L	Patients carrying two abnormal AAT genes. Most studies do not show an increased risk of disease. It is unclear whether there is a risk of getting disease symptons.
SZ	Alpha-1	16.5 (10-23) µmol/L	**Severe deficiency** — patients carrying two abnormal AAT genes. They could get the disease.
ZZ	Alpha-1	5.3 (3.4-7) µmol/L	**Severe deficiency** — patients carrying two abnormal AAT genes. They could get the disease.

EXAMPLE OF HOW ALPHA-1 IS INHERITED

Delaying the diagnosis of AATD is linked with **worsened outcomes for patients**, for example, the deterioration of lung function. This is why it is important to encourage testing even in patients who currently show no symptoms yet.[11,16]



Early intervention offers many benefits, such as access to preventive measures, pharmacological and non-pharmacological treatments.[17]

THE BENEFITS OF TESTING FOR ALPHA-1

Of the estimated **116 million carriers** of alpha-1 alleles worldwide, **3.4 million people have the disease alleles (S and Z)** and have or will develop the disease.[4] However, **90% of patients are still not being correctly diagnosed**.[4,18]

Accurate and early diagnosis of patients is critical for:[4,18]

- Providing **specific clinical care**
- **Slowing the progression** of tissue deterioration
- **Effectively managing** the disease

The guideline recommendation is to screen all COPD patients for AATD.[17,19-21] A negative test allows you to rule out alpha-1 as a root cause of disease and focus on other possible factors.

WHO CAN BENEFIT FROM BEING TESTED FOR ALPHA-1?

As alpha-1 is a hereditary autosomal co-dominant genetic condition, it **can also affect family members**.[18]

Testing is recommended for **immediate family members** including parents, siblings, offspring, and any other **at-risk extended family members** presenting AATD-related conditions, such as chronic liver disease, panniculitis, bronchiectasis, granulomatosis with polyangiitis or COPD.[11]

Testing for alpha-1 will help to expose if the family is at risk.

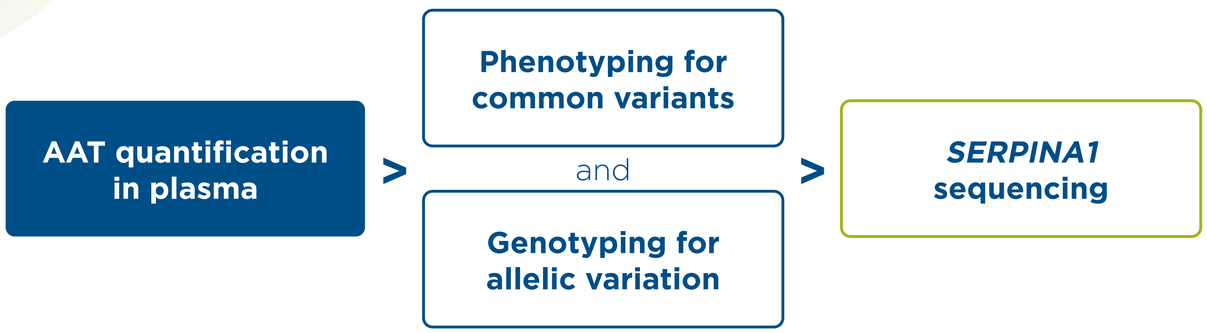
STEPS IN THE TESTING JOURNEY

Testing for AATD combines a few different screening methods:[22]

- **Quantitative measurement of AAT** is performed by nephelometric determination. It is **not costly** and results are typically reported as µmol/L or mg/dL, with **20–53 µmol/L** or **100–220 mg/dL** within the **normal range**.[3,11]

Further confirmation tests for pathological allelic variants are required since serum protein levels alone may not detect carriers, i.e. heterozygous people for the Z allele:[3]

- **Phenotype studies** are based on the migration speed of the resulting protein on isoelectric focusing. However, **phenotype alone is not sufficient** to elucidate the allelic variant.[10,22]
- **Genotyping** could be performed through blood tests, dried blood spot (DBS), or **buccal swab** test. The allele-specific genotyping assay is used for the **detection of the S and Z alleles** and more rare variants.[23]
- **Direct sequencing of the *SERPINA1* region** is the last resource when both alleles are unable to be identified.[23]



Testing for alpha-1 is simple and helps to slow down disease progression.

LIFESTYLE RECOMMENDATIONS FOR PATIENTS WITH ALPHA-1

Patients and their family can benefit from behavioral and lifestyle recommendations. Review the following suggestions with your patient:[17,24]

Quit smoking and avoid second-hand smoke

Click for more info

Consume alcohol with caution, if at all

Click for more info

Avoid exposure to occupational and environmental pollutants

Click for more info

Create a nutrition programme

Click for more info

Develop an exercise program

Click for more info

Maintain mental health and well-being

Click for more info

LIFESTYLE RECOMMENDATIONS FOR PATIENTS WITH ALPHA-1

Patients and their family can benefit from behavioral and lifestyle recommendations. Review the following suggestions with your patient:[17,24]

Quit smoking and avoid second-hand smoke

Close

Smoking significantly increases the risk and severity of emphysema and decreases the lifespan considerably.

Consume alcohol with caution, if at all

Avoid exposure to occupational and environmental pollutants

Create a nutrition programme

Develop an exercise program

Maintain mental health and well-being

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Consume alcohol with caution, if at all

− Close

If there is any indication of liver damage, alcohol should be avoided completely.

Avoid exposure to occupational and environmental pollutants

Create a nutrition programme

Develop an exercise program

Maintain mental health and well-being

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Consume alcohol with caution, if at all

Avoid exposure to occupational and environmental pollutants

Close

Particle pollution can irritate the lungs and cause or worsen lung problems. It can also be absorbed through the skin and thus damage the liver.

Create a nutrition programme

Develop an exercise program

Maintain mental health and well-being

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Consume alcohol with caution, if at all

Avoid exposure to occupational and environmental pollutants

Create a nutrition programme

Close

Sodium and protein intake may become a concern because fluid retention is common. This should be checked with the help of a nutritionist.

Develop an exercise program

Maintain mental health and well-being

LIFESTYLE RECOMMENDATIONS FOR PATIENTS WITH ALPHA-1

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Consume alcohol with caution, if at all

Avoid exposure to occupational and environmental pollutants

Create a nutrition programme

Develop an exercise program

Close

It is important to exercise muscles in the chest and upper body that are related to breathing as well as the large muscles of the legs.

Maintain mental health and well-being

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Avoid exposure to occupational and environmental pollutants

Create a nutrition programme

Develop an exercise program

Maintain mental health and well-being

Close

Learning relaxation techniques can help to have a more optimistic outlook on life and may prevent depression.

TREATMENT OPTIONS FOR PATIENTS WITH ALPHA-1

VACCINATIONS

Consider the following vaccines for your patient:

- Hepatitis A and B.[3]
- Influenza, polysaccharide pneumococcal, protein-conjugated pneumococcal and COVID-19.[18]

LIVER DISEASE

- **Reduction and/or cessation of alcohol** and hepatotoxic agents.[3]
- **Nonselective β-blockers** or **endoscopic band ligation** therapy: management of varices.[3]
- **Low-salt diet, diuretics** and **paracentesis**: for ascites.[3]
- **Nutrition advice and support**: for patients with cirrhosis.[3]
- **Portal vein decompression**: to reduce blood vessel pressure, improving outcomes.[25]
- **Transplant**: for the more severe cases.[18]

TREATMENT OPTIONS FOR PATIENTS WITH ALPHA-1

LUNG DISEASE

- **Bronchodilators and anti-inflammatory therapy**: inhaled corticosteroids, to improve and relieve airway obstruction and reduce inflammation.[18]
- **Oral corticosteroid supplemented with oxygen**: in case of exacerbations.[18]
- **Antibiotics**: to reduce respiratory infections and potential tissue damage.[18]
- **Dapsone or doxycycline therapy**: for panniculitis treatment.[11]
- **Surgery**: removal of the damaged tissue (lung volume reduction surgery).[26]
- **Transplant**: considered for worse prognostic cases (end-stage lung).[11,18]

OTHER APPROACHES

Gene editing and **stem cell therapy**: ongoing research.[10,18]

Although AATD can be effectively managed to alleviate symptomatology, the only approach that fully addresses AATD is augmentation therapy.[18]

WHAT IS AUGMENTATION THERAPY?

- In order to reduce neutrophil elastase damage, **AAT administration** in severely deficient patients slows the progression of lung tissue damage and emphysema development, respiratory decline, and terminal respiratory events.[3,17,18]
- However, it is **not indicated for patients with liver disease**.[3]
- **Augmentation therapy** consists of the administration of weekly intravenous human AAT at a dosage of **60 mg/kg** of body weight.[11,18]
- These infusions are **administered by healthcare professionals** at home, at an outpatient infusion centre or another medical facility. The patient could also choose to self-infuse at home after receiving appropriate instruction and approval from a healthcare professional.

TO CONSIDER BEFORE ADMINISTRATION

- Augmentation therapy is contraindicated in patients that are **IgA deficient** due to anaphylaxis concerns; for this reason, IgA levels are tested before treatment administration.[27]
- **Vaccination against hepatitis A and B** is also recommended to reduce the risk of liver injury.[3]

POSSIBLE SIDE EFFECTS

- Augmentation therapy is generally considered a **safe procedure with minimal side effects**.[28]
- Reported side effects are usually **mild to moderate** and do not interfere with the treatment or require major procedures.[28]
- **The most common side effects** reported are:[28]
  - Headache
  - Dizziness
  - Fever or chills
  - Urticaria
  - Nausea or vomiting
  - Fatigue
  - Dyspnea

These symptoms can often be reduced or eliminated by slowing the rate of infusion.[28]

SURVEILLANCE

All treatments are accompanied by **surveillance tests every 6-12 months**, including spirometry with bronchodilators, diffusing capacity measurements, liver function tests, etc.[11]

HELP YOUR PATIENTS FIND ADDITIONAL SUPPORT TO ADDRESS THEIR REMAINING CONCERNS

Whether your patients are thinking about getting tested or have already been diagnosed, there is more helpful information available for them.

The area where they live may have support groups and/or patient organisations that can offer them guidance and support. Patient organisations are the best place to share experiences and to learn more about living with AATD.

Make sure they know all the available resources!

Find out if there is a support organisation in their country here:
www.alpha-1global.org

Additional information and resources about alpha-1 can be found here:
https://www.alpha1.org/

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GRIFOLS

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