



## Genetic Testing for Alpha-1 Antitrypsin Deficiency

**Effective:** September 1, 2026

**Next Review:** May 2027

**Last Review:** July 2026

### IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

### DESCRIPTION

Alpha-1 antitrypsin deficiency (AATD) is an autosomal disorder which may result in increased risk of liver and/or lung disease, especially in smokers or in patients with other environmental exposures.

### MEDICAL POLICY CRITERIA

Genetic testing for alpha-1 antitrypsin deficiency is considered **investigational** for all indications.

*NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.*

### CROSS REFERENCES

1. [Genetic and Molecular Diagnostic Testing](#), Genetic Testing, Policy No. 20

### BACKGROUND

Alpha-1 antitrypsin deficiency (AATD) is an autosomal recessive genetic disorder that results in decreased production of the alpha-1 antitrypsin (AAT) protein, or production of abnormal

types of the protein that are functionally deficient. Data from screening studies have found the prevalence of AATD in North America to be between 1 in 5,000 and 1 in 7,000 individuals.<sup>[1]</sup> Individuals with AATD, especially smokers, have an increased risk of lung and liver disease. Tests are available to measure serum AAT levels and for AAT protein variant phenotyping. Genetic testing is also available to detect the most common variants associated with AATD.

AAT is an acute phase glycoprotein, synthesized primarily in the liver and secreted into the bloodstream. One of the primary functions of the AAT protein is to protect the lungs from damage by the enzyme elastase. Elastase, part of the normal response to injury and inflammation, breaks down proteins but can also break down and damage lung tissue if its action is not regulated by AAT. Therefore, individuals with AAT deficiency have an increased risk of lung disease.

Respiratory disease tends to be more severe and occur sooner (i.e., between age 40 and 50) in individuals with AAT deficiency who smoke cigarettes and/or are exposed to occupational dust or fumes. In non-smokers and individuals without environmental exposure, onset of respiratory disease occurs more commonly in the sixth decade. Childhood-onset lung disease is rare with AATD. AATD is also associated with an increased risk of liver disease, thought to occur due to aggregation of damaged AAT in the liver cells, where the protein is produced. The most common manifestation of liver disease in childhood is jaundice. Adult-onset liver disease generally manifests as cirrhosis and fibrosis. Necrotizing panniculitis is a rare, but a well-recognized complication of AAT deficiency. This dermatological condition is characterized by inflammatory and necrotizing lesions of the skin and subcutaneous tissue.<sup>[1]</sup>

The primary interventions to prevent or treat symptoms in individuals with AATD involve behavioral change, especially avoiding or quitting cigarette smoking. Smoking is the most important risk factor for the development of emphysema in AATD individuals who are homozygous for the most severe AAT variants.<sup>[2]</sup> In addition, individuals with AATD are advised to avoid other substances that can cause liver damage. There are also general recommendations to exercise, avoid stress, and have a nutritious diet. Furthermore, more aggressive treatments for conditions such as asthma outbreaks or acute exacerbations of chronic obstructive pulmonary disease (COPD) may be recommended for patients with AATD. One treatment option that is specific to AATD is AAT augmentation. Patients generally receive injections of plasma every three to four weeks for life; however, there is a lack of consensus about the efficacy of this treatment.<sup>[3]</sup>

## **DIAGNOSTIC TESTING FOR ALPHA-1 ANTITRYPSIN DEFICIENCY (AATD)**

Several types of tests are available for patients who are suspected of having AATD. A blood test is available that quantifies the total amount of AAT in the blood, detecting decreases in AAT protein levels, but not distinguishing among abnormal protein types. AAT is an acute phase reactant, and levels will be elevated in acute and chronic inflammatory conditions, infections, and some cancers, which may cause levels to appear normal in individuals with mild to moderate AAT deficiency. In general, a serum concentration of AAT less than 15% to 20% of the normal value is highly suggestive of a homozygous AAT variant.<sup>[4]</sup>

Genetic testing is also available for patients suspected of having AATD. Production of AAT is encoded by the *SERPINA1* gene, which is co-dominant (each gene copy is responsible for producing half of the AAT). Although there are more than 75 sequence variants of the *SERPINA1* gene (i.e., 75 possible alleles), only a few are common in North America. Approximately 95% of individuals have two copies of the normal M allele sequence (MM,

PiMM) and have mean serum concentrations of AAT ranging from 20 to 53  $\mu\text{mol/L}$ . The most common abnormal forms are the Z allele and the S allele. Individuals with two copies of the Z allele (ZZ, PiZZ) tend to be most severely affected, characterized by mean serum concentrations of AAT between 2.5 to 7  $\mu\text{mol/L}$  and a high risk of COPD. Individuals with rarer variants of the *SERPINA1* gene or null alleles may not produce any AAT and are also at high risk.<sup>[5]</sup> Individuals with genotype SS (PiSS) and heterozygous individuals with genotype MZ (PiMZ) have low risk of COPD and moderately lower levels of AAT.

Genetic testing for AATD is most commonly done by the alpha-1 genotype test. This test uses polymerase chain reaction (PCR) analysis, or some other type of nucleic acid-based analysis, to identify abnormal alleles of AAT DNA. Currently, genotype tests are only designed to detect the most common variants, i.e., the S and Z alleles.

A common approach to testing for AATD is to perform serum quantitation. If the AAT level is found to be low, a follow-up phenotype or genotype test is ordered. Another approach is to perform serum protein quantification, followed by genotype testing in individuals with clinical suspicion of AATD. If these tests are discordant, phenotype testing is then performed.

## REGULATORY STATUS

An example of a U.S. Food and Drug Administration (FDA)-cleared phenotyping test is the Hydragel 18 alpha-1 antitrypsin (A1AT) ISOFOCUSING kit (Sebia Inc.). In 2007, this test was cleared for marketing through the 510(k) process. The test is designed for the qualitative detection and identification of the phenotypes of AAT protein.

No FDA-cleared genotyping tests were identified. Thus, genotyping is offered as a laboratory-developed test. Clinical laboratories may develop and validate tests in-house (“home-brew”) and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The laboratory offering the service must be licensed by CLIA for high-complexity testing.

## EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature<sup>[6]</sup> is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term “variant” is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as “mutation.” Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

Validation of the clinical use of any genetic test focuses on three main principles:

1. Analytic validity, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent;
2. Clinical validity, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. Clinical utility, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

The focus of this evidence review is the clinical validity and utility of genetic testing for

AATD.

## CLINICAL VALIDITY

Lopez-Campos (2022) conducted an observational analysis of A1AT genotyping test results from 30,827 samples collected via buccal swab from patients with suspected AATD in Argentina, Brazil, Chile, Colombia, Spain, and Turkey.<sup>[7]</sup> The swabs were sent to a central laboratory for analysis. COPD was the most common reason for suspected AATD (49.4%), followed by poorly controlled asthma (11.0%), and bronchiectasis (4.7%). One-quarter of patients tested had no documented reason for AATD genetic screening. Gene mutations were identified in 30.9% of samples. The following genotypes were reported: MS (14.7%), MZ (8.6%), SS (1.9%), SZ (1.9%), and ZZ (0.9%).

A study published by da Costa (2019) assessed the results of AATD screening in COPD patients in Brazil.<sup>[8]</sup> AAT levels in 551 patients were measured by immunonephelometry, with confirmation of AATD by molecular testing. Forty of these patients had a genetic variant, with 11 having the PiZZ genotype. Spirometric measurements were similar between those with and without AATD.

Greulich (2017) reported on genetic testing results for patients in central-eastern Europe suspected of having severe AATD.<sup>[9]</sup> The AAT concentration was determined by nephelometry in 11,648 patients from 13 countries. Samples with AAT values lower than 1.70 mg/dL in dried blood spot (n=1,404) were sent for genetic testing. Polymerase chain reaction was used to detect the PiS and PiZ alleles. Eighty-one percent of the samples were negative for S and Z alleles; 71 (5%) were identified as PiS, 151 (11%) were PiZ, 1 (<0.1%) was PiSS, 8 (<1%) were PiSZ, and 32 (2%) were PiZZ. Isoelectric focusing was used for phenotyping in 1363 samples identified as non-S and non-Z by genotyping and had sufficient sample for additional testing. Of these, 1053 (77%) were identified as PiMM, 71 (5%) were PiMS, 144 (11%) were PiMZ, three (<0.5%) were PiM, two (<0.5%) were PiZ, and two (<0.5%) were Pi(null)(null).

Greulich (2016) reported results of a large AATD screening program in Germany.<sup>[10]</sup> The targeted screening strategy undertaken in this study combined initial measurement of serum AAT level and a PCR test to detect the Z and S alleles, followed by genetic sequencing, if necessary. The authors additionally performed untargeted screening at events, typically patient organization meetings, where all individuals could be tested, regardless of symptoms or AAT levels. Between 2003 and 2015, 19,121 test kits were received by the laboratory, of which, 18,683 were eligible for study inclusion (targeted strategy n=17,635; general screening n=1,048). There were 6,919 (37.1%) individuals with at least one pathogenic allele and 1,835 (9.8%) with AATD found during this period, and the strongest predictors of the ZZ genotype were emphysema, COPD, and bronchiectasis. The targeted screening identified a significantly higher proportion of individuals with AATD than the general event-based screening.

Sorroche (2015) conducted a cross-sectional study of 1,002 COPD patients. Serum levels of AAT were obtained and, for patients found to have low serum AAT ( $\leq 100$  mg/dL), genotyping using PCR was performed.<sup>[11]</sup> A total of 217 patients had AAT levels of 100 mg/dL or less and underwent genotyping. Genotyping detected 15 patients with genotypes (SZ or ZZ) associated with severe AATD, 29 Z heterozygotes, 25 S heterozygotes and four SS. A total of 144 (66%) of the 217 patients with low AAT levels had discrepant findings between serum level testing and genotyping but were lost to follow-up and did not undergo additional testing (i.e., phenotyping).

Beletic (2014) performed genotyping using direct sequencing in 50 patients diagnosed with COPD before the age of 45.<sup>[12]</sup> The authors found that genotyping did not identify more AATD patients than using AAT concentrations alone. The authors did not report sensitivity or specificity.

Ljubic (2008) published findings of a study with 27 emphysema patients.<sup>[13]</sup> Phenotyping was performed using isoelectric focusing and genotyping by denaturing gradient gel electrophoresis. Isoelectric focusing was successfully performed in 25 cases and genotyping results were available for all 27 patients. Phenotyping and genotyping were concordant for the four patients found to have one or two 'Z' alleles. However, genotyping found two unusual pathogenic variants and in both of these cases, normal protein phenotypes were found. The authors found that genotyping did not identify more AATD patients than AAT concentrations alone.

The FDA decision summary for the Hydragel phenotyping test included an evaluation of clinical sensitivity and specificity.<sup>[14]</sup> Samples were evaluated from 64 patients with the following diagnoses: congenital AATD (n=16), pulmonary disorder (n=15), hepatic disorder (n=8), infertility (n=1), panniculitis (n=1) and normal (n=23). The sensitivity of the phenotype test was 39/39 (100%) and the specificity was 23/25 (92%). (Note: This analysis excluded four individuals with indeterminate diagnoses).

## CLINICAL UTILITY

The clinical utility of genetic testing for AATD depends on how the results can be used to improve patient management. With AATD, this could occur in several ways, including the following:

- Patient knowledge of AAT status could lead to behavior change that improves health outcomes. Specifically, asymptomatic smokers could quit smoking which may prevent or delay onset of lung disease, and symptomatic smokers could quit smoking which may prevent progression of lung disease. Knowledge of AAT status could also lead to other behavioral changes including avoiding pollutants, increasing exercise, avoiding alcohol, and avoiding smoking for those who have not started.<sup>[15]</sup>
- A diagnosis of AATD could lead to changes in treatment, which may improve patient outcomes. The only treatment specific to AATD is AAT augmentation therapy. In addition, the intensity and/or timing of other treatments may be different for individuals with known AATD. This includes antibiotic treatments for lung infections and vaccinations (influenza, pneumococcus, hepatitis A and B, etc.).<sup>[2]</sup>

## Smoking Cessation

In 2003, the American Thoracic Society (ATS) and the European Respiratory Society (ERS) published a joint statement on diagnosis and management of AATD, based on systematic reviews and an evidence-based approach to evaluating published data.<sup>[2]</sup> A review of smoking cessation studies in the ATS/ERS joint statement did not identify any randomized controlled trials (RCTs) on the impact of AATD status on smoking cessation. However, an RCT on a related topic was identified which found that, at one year, individuals who received genetic susceptibility information (in this case, *CYP2D6* genotype results) were significantly more likely to report a quit attempt than individuals who received counseling only, although quit rates did not differ significantly in the two groups.<sup>[16]</sup>

Ashenhurst (2022) published the results of a self-reported survey of lifestyle and behavior changes among individuals who received direct to consumer genetic test results (23andMe®, which evaluates Z and S alleles).<sup>[17]</sup> Among the 205,632 survey participants, 195,014 were analyzable. Of these, 0.63% had self-reported physician-diagnosed AATD, many of whom were diagnosed after they shared their genetic results with their physician. Individuals with a ZZ genotype shared their results with a health care provider or family member in 51.1% and 79.9% of cases, respectively. Individuals with an SZ genotype shared their results with a health care provider or family member in 27.5% and 59.6% of cases, respectively. Individuals with heterozygous Z variants were more likely to report a decrease in smoking (odds ratio 1.7,  $p < 0.0015$ ) and individuals with homozygous Z variants were more likely to report a decrease in alcohol consumption (odds ratio 3.9,  $p < 0.0015$ ) than individuals without Z variants.

Carpenter (2007) reported on findings of a survey of individuals who had volunteered for genetic testing for AATD.<sup>[18]</sup> A total of 4,344 individuals completed a test kit; 331 (7.6%) respondents were rejected because their blood sample was insufficient. The remaining participants were mailed a follow-up letter with their test results and a genotype-specific brochure. Results of the testing revealed that 2,228 (56%) of the valid samples tested normal, 1,530 (38%) were found to be heterozygous carriers for AATD (MZ genotype) and 255 (6%) were found to be severely AAT deficient (SZ or ZZ genotype). A total of 729/2,228 (33%) of participants with valid blood samples identified themselves as current cigarette smokers. These smokers were sent an additional questionnaire three months after the initial letter. Test results among smokers were 55% normal genotype, 38% carrier and 7% severely AAT deficient. Of the 729 surveys sent to smokers, 205 (28%) were completed. Six smokers were excluded because they smoked less than six cigarettes per day, leaving 199 participants in the study sample. Survey responders were more likely to be older than non-respondents. Authors reported that there were no significant differences in response rates by genotype group. Among survey respondents, individuals with severe AATD were significantly more likely to make any self-reported quit attempt than were individuals with a normal genotype (59% vs. 33%,  $p < 0.05$ ). Of eight quit behaviors listed in the survey, AAT deficient smokers reported engaging in a mean of 2.4 (standard deviation [SD]=2.3). This was significantly higher than the number of quit behaviors reported by carriers (0.7, SD=1.3) or non-carriers (1.3, SD=2.0,  $p = 0.04$ ). There was not a significant difference between groups, however, in the abstinence rate at three months (defined as 24-hour point prevalence). This study was limited in that it lacked a control group of smokers who were not tested for AATD. In addition, the low response rate made conclusions difficult regarding the behavior of smokers who were identified as having moderate or severe AATD. Overall, evidence is lacking regarding the impact of AAT status on smoking cessation. Large randomized controlled trials comparing cessation rates in patients with and without AAT testing are needed in order to determine whether knowledge of AAT status significantly impacts patient health decisions.

## Smoking Prevention

The ATS/ERS joint statement on AATD noted two case-control studies that included children identified at birth as having AATD and matched to a demographically similar control group.<sup>[19, 20]</sup> The number of children with AATD was 61 in one study and 22 in the other. These studies reported a lower frequency of adolescent smoking in individuals identified at birth as having AAT deficiency, compared to the control individuals.<sup>[21]</sup> These studies are limited in number and by small sample size which make conclusions regarding the clinical significance of AAT status on smoking prevention uncertain. In addition, neither of these two studies performed long-term

follow-up on the AATD affected group past the single survey of smoking attitudes and rates in early adolescents (around 18 to 20 years of age). Comparative studies between children with and without AATD who have received testing are needed to determine whether anti-smoking attitudes and lower smoking rates are sustained over time.

## **Treatment for Individuals with AATD**

### Alteration of Timing or Intensity of Treatments for Patients with AATD

The ATS/ERS recommendations for treating AATD patients with pulmonary disease are the same as the recommendations for patients with COPD, in general.<sup>[2]</sup> No controlled studies specific to AATD were cited in support of these recommendations to determine whether the timing, intensity, or compliance with these treatments is altered by knowledge of AATD status.

The 2016 Alpha-1 Foundation guidelines state that, "There are no reliable data to suggest a differential treatment response to bronchodilators, inhaled corticosteroids, pulmonary rehabilitation, supplemental oxygen therapy, or immunizations in individuals with AATD-COPD and AAT-replete COPD."<sup>[21]</sup>

### Alpha-1 Antitrypsin Augmentation Therapy

A 2016 Cochrane review addressed the benefits and harms of augmentation therapy with AAT in patients with AATD and lung disease.<sup>[22]</sup> Three RCTs comparing AAT augmentation therapy to placebo were identified; all included patients with genetic variants associated with a high risk of developing COPD. Primary outcomes of the review were mortality and adverse effects of the intervention. Data on these outcomes were not available for pooling. Meta-analyses were conducted on several secondary outcomes. A pooled analysis of the three studies did not find a significant difference in FEV<sub>1</sub> deterioration over the course of the studies in the treatment compared with the placebo group. The pooled standardized mean difference (SMD) in FEV<sub>1</sub> was -0.19 (95% confidence interval [CI] -0.42 to 0.05, p=0.12). There was also no significant difference between groups in change in carbon monoxide diffusion (SMD = -0.11, 95% CI -0.35 to 0.12, p=0.34). However, a pooled analysis of lung density change (in grams per liter) according to CT findings favored the treatment group. The mean difference was 0.86 (95% CI 0.31 to 1.42, p=0.004). Authors concluded there were insufficient data to draw conclusions about the impact of AAT augmentation therapy on health outcomes.

No additional RCTs evaluating the impact of AAT augmentation therapy on health outcomes in patients with AATD have been published since the 2010 Cochrane review.

## **SECTION SUMMARY**

Limited evidence suggests knowledge of AATD status may lead to more quit attempts but not higher smoking cessation rates. There is also limited evidence from two small case-control studies suggesting that individuals who know from birth they have AATD, are less likely to initiate smoking than individuals without genetic testing information. However, these studies are limited by short-term follow-up which preclude conclusions regarding the long-term impact of AAT testing status on smoking prevention.

The only AATD-specific treatment is AAT augmentation therapy, which is often prescribed for patients with documented AATD and COPD. A Cochrane review concluded that the evidence base is insufficient to determine whether AAT augmentation therapy is effective for improving health outcomes in individuals with AATD.

### ALPHA1-FOUNDATION

In 2016, the Alpha-1 Foundation made the following recommendations for AATD testing:<sup>[21]</sup>

- All individuals with COPD regardless of age or ethnicity should be tested for AATD.
- All individuals with unexplained chronic liver disease should be tested for AATD.
- All individuals with necrotizing panniculitis, granulomatosis with polyangiitis, or unexplained bronchiectasis should be tested for AATD.
- Parents, siblings, and children, as well as extended family of individuals identified with an abnormal gene for AAT, should be provided genetic counseling and offered testing for AATD (see guideline document for special considerations about testing minors).
- For family testing after a proband is identified, AAT level testing alone is not recommended because it does not fully characterize disease risk from AATD.
- For diagnostic testing of symptomatic individuals, we recommend genotyping for at least the S and Z alleles. Advanced or confirmatory testing should include Pi-typing, AAT level testing, and/or expanded genotyping.

The guidelines recommend the use of augmentation therapy in individuals with an FEV1 less than or equal to 65% predicted or necrotizing panniculitis. They recommend discussion of augmentation therapy in individuals with an FEV1 greater than 65% regarding the potential benefits of reducing lung function decline with consideration of the cost of therapy and lack of evidence for such benefit.

### AMERICAN THORACIC SOCIETY AND THE EUROPEAN RESPIRATORY SOCIETY

In 2003, the American Thoracic Society (ATS) and the European Respiratory Society (ERS) published a joint statement with recommendations on the diagnosis and management of individuals with AAT deficiency.<sup>[2]</sup> Of note, the ATS and ERS issued these recommendations with grading classifications, and stated that, “each recommendation type was based on the level of supportive evidence for each issue regarding testing.” However, the quality of the evidence used to assign grades to these recommendations was not clearly defined within the joint statement.

#### Recommendations were classified as follows:

Type A: Genetic testing is recommended

Type B: Genetic testing should be discussed and could be accepted or declined

Type C: Genetic testing is not recommended i.e., should not be encouraged

Type D: Recommend against genetic testing i.e., should be discouraged

- Type A recommendations for diagnostic testing in the following situations:
  - Symptomatic adults with emphysema, COPD or asthma with airflow obstruction that is not completely reversible with aggressive treatment with bronchodilators;
  - Individuals with unexplained liver disease
  - Asymptomatic individuals with persistent obstruction on pulmonary function tests

- with identifiable risk factors (e.g. cigarette smoking, occupational exposure)
  - Adults with necrotizing panniculitis
  - Siblings of an individual with known alpha-1 antitrypsin (AAT) deficiency
- Type B recommendations for diagnostic testing in the following situations:
  - Adults with bronchiectasis without evidence etiology
  - Adolescents with persistent airflow obstruction
  - Asymptomatic individuals with persistent airflow obstruction and no risk factors
  - Adults with C-ANCA positive (anti-proteinase 3-positive) vasculitis
  - Individuals with a family history of COPD or liver disease not known to be attributed to AAT deficiency
  - Distant relatives of an individual who is homozygous for AAT deficiency
  - Offspring or parents of an individual with homozygous AAT deficiency
  - Siblings, offspring, parents, or distant relatives of an individual who is heterozygous for AAT deficiency
  - Individuals at high risk of having AAT deficiency-related diseases
  - Individuals who are not at risk themselves of having AAT deficiency but who are partners of individuals who are homozygous or heterozygous for AAT deficiency
- Type C recommendations for diagnostic testing in the following situations:
  - Adults with asthma in whom airflow obstruction is completely reversible
  - Predispositional testing
  - Population screening of smokers with normal spirometry
- Type D recommendations for diagnostic testing in the following situations:
  - Predispositional fetal testing
  - Population screening of either neonates, adolescents, or adults

## SUMMARY

There is not enough research to show that genetic testing for alpha-1 antitrypsin deficiency (AATD) can improve health outcomes for individuals with any condition. Therefore, genetic testing for AATD is considered investigational for all indications.

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## CODES

| Codes | Number | Description                                                                                                                                                                                     |
|-------|--------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| CPT   | 81332  | <i>SERIPINA 1</i> (serpin peptidase inhibitor, clade A, alpha-1 antiproteinase, antitrypsin, member 1) (e.g., alpha-1-antitrypsin deficiency), gene analysis, common variants (e.g., *S and *Z) |
| HCPCS | None   |                                                                                                                                                                                                 |

**Date of Origin:** May 2013