
Medical Policy



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(See policy history boxes for previous effective dates)

Title: Genetic Testing for Alpha₁-Antitrypsin Deficiency

Description/Background

ALPHA₁-ANTITRYPSIN DEFICIENCY

Alpha₁-antitrypsin deficiency (AATD) is an autosomal recessive genetic disorder that decreases the production of functional alpha₁-antitrypsin (AAT) protein, or results in production of abnormal types of the protein that are functionally deficient. Data from screening studies have found the prevalence of AATD in the United States to be between 1 in 2,857 and 1 in 5,097 individuals.(1)

AAT is an acute phase glycoprotein, primarily synthesized 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 and can damage lung tissue if its action is not regulated by AAT. Individuals with AATD thus have an increased risk of lung disease.

Alpha₁-Antitrypsin Deficiency Genetics

Production of AAT is encoded by the *SERPINA1* gene, which is codominant (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 2 copies of the normal M allele sequence (MM) and have mean serum AAT concentrations ranging from 20 to 53 µmol/L. The most common abnormal forms are the Z and the S alleles. Individuals with 2 copies of the Z allele (ZZ) tend to be most severely affected, with mean serum AAT concentrations of 2.5 to 7 µmol/L and a high risk of chronic obstructive pulmonary disease (COPD). Individuals with genotype SS and heterozygous individuals with genotype MZ have low risk of COPD and moderately lower levels of AAT. Individuals with rarer pathogenic variants of the *SERPINA1* gene or null alleles may not produce any AAT and are also at high risk.(2)

Clinical Presentation

AATD is a multisystem disease, primarily affecting the lungs and liver, and less commonly the skin. It may present differently at different ages.

Pulmonary Manifestations

Respiratory disease tends to be more severe and occur sooner (i.e., between ages 40 and 50 years) in individuals with AAT deficiency who smoke cigarettes and/or are exposed to occupational dust or fumes. In nonsmokers and individuals without environmental exposure, onset of respiratory disease occurs more commonly in the sixth decade. Childhood-onset lung disease is rare with AATD.

Liver Manifestations

Adults with AATD-associated liver disease generally present with cirrhosis and fibrosis. In contrast, newborns with AATD can present with cholestasis or (less frequently) hepatomegaly and elevated aminotransferase levels. The AATD-associated cholestasis is typically associated with PI*Z homozygotes or PI*SZ heterozygotes, which tend to have less severe lung disease in adulthood. AATD-associated-cholestatic jaundice can progress to require liver transplant in newborns. In a large series of 127 newborns with AATD found by screening, the prevalence of liver damage was 11%, severe in about two-thirds of cases.(3)

Skin Manifestations

Panniculitis is a rare, but well-recognized complication of AATD. This dermatologic condition is characterized by inflammatory and necrotizing lesions of the skin and subcutaneous tissue.(4)

Clinical Management

The primary interventions to prevent or treat lung-related symptoms in adults 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 in individuals who are homozygous for the most severe AAT pathogenic variants.(1) In addition, individuals with AATD are advised to avoid other substances that can irritate the lungs (e.g., cigarette smoke, dust, workplace chemicals), as well as substances that can cause liver damage (e.g., alcohol). There are also general recommendations to exercise, avoid stress, and have a nutritious diet. Furthermore, patients with AATD may be recommended to have earlier or more aggressive treatments for conditions such as asthma outbreaks or acute exacerbations of chronic obstructive pulmonary disease (COPD). One treatment option that is specific to AATD is AAT augmentation. There are commercially available intravenous AAT augmentation products; patients generally receive injections of plasma every 3 to 4 weeks for life. Inhaled AAT augmentation therapy is under development. There is no consensus on the efficacy of augmentation treatment. Product labels state that the effect of augmentation therapy on emphysema progression and pulmonary exacerbations has not been demonstrated in randomized controlled trials.(5,6)

Other aspects of management of AATD involve monitoring for and screening for comorbidities, including liver disease.

Diagnostic Testing for Alpha₁-Antitrypsin

Several types of tests are available for patients 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 AATD. In general, a serum AAT concentration less than 15% to 20% of the normal value is highly suggestive of a homozygous AAT pathogenic variant.(7)

The alpha₁ phenotype test identifies the type of circulating AAT protein in the blood by isoelectric focusing of the various AAT protein types. Patterns of protein migration in an electric field are evaluated and compared with normal patterns to determine if and what type of abnormal AAT protein may be present.

Genetic testing for AATD can be done with the alpha₁ genotype test. This test uses polymerase chain reaction analysis or nucleic acid–based analysis to identify abnormal alleles of AAT DNA. Currently available genotype tests are only designed to detect the most common pathogenic variants (i.e., S and Z alleles).

There are several testing approaches to detect AATD. One is to initially perform serum quantitation and then, 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 subjects with clinical suspicion of AATD. If these tests are discordant, phenotype testing is then performed.

Regulatory Status

In 2007, the phenotyping test Hydragel 18 A1AT ISOFOCUSING kit (Sebia, GA) was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process for the qualitative detection and identification of the phenotypes of alpha₁-antitrypsin protein. In 2022, the SPIFE A1AT phenotyping kit (Helena Laboratories) was approved by the FDA by the 510(k) process for the same indication. In 2017, the A1AT Genotyping Test (Grifols) was approved by the FDA as an aid to diagnosis of individuals with AATD. FDA product code: OBZ, PZH.

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, FDA has chosen not to require any regulatory review of this test. Molecular diagnostic laboratories may also be accredited by the College of American Pathologists Laboratory Accreditation Program. To date, FDA has chosen not to require any regulatory review of this test.

Medical Policy Statement

The effectiveness and clinical utility of genetic testing for alpha₁-antitrypsin deficiency have been established. It may be considered a useful diagnostic option when indicated.

Inclusionary and Exclusionary Guidelines

The diagnosis of alpha₁-antitrypsin deficiency first requires assessment of the phenotype and serum concentrations of alpha₁-antitrypsin protein. Genetic testing for alpha₁-antitrypsin deficiency is indicated in the following:

Inclusions:

1. The individual is suspected of having AAT deficiency because of clinical factors* and/or because the individual may be at high risk of having AAT deficiency due to a first-degree relative** with AAT deficiency; **OR**
2. A discrepancy exists between an individual’s AAT level and his or her phenotype (e.g. an individual who has an AAT deficiency despite having a normal phenotype); **OR**
3. The individual’s clinical presentation is unusual (as in early onset pulmonary emphysema with a normal AAT level).

*Clinical factors:

- Early-onset emphysema (age of 45 years or less)
- Emphysema in the absence of a recognized risk factor (smoking, occupational dust exposure, etc.)
- Emphysema with prominent basilar hyperlucency
- Otherwise unexplained liver disease
- Necrotizing panniculitis
- Anti-proteinase 3-positive vasculitis (C-ANCA [anti-neutrophil cytoplasmic antibody]-positive vasculitis)
- Bronchiectasis without evident etiology

**Family history

- A first-degree relative is defined as a parent, child, or sibling.

***Serum AAT Level

Table PG1 shows the range of serum levels of alpha₁-antitrypsin by common phenotypes according to the commercial standard milligram per deciliter and the purified standard micromole. A level less than 11 μmol is generally considered to be associated with an increased risk of clinical disease, but this cutoff may vary by the specific test used (American Thoracic Society & European Respiratory Society, 2003; Global Initiative for Chronic Obstructive Lung Disease, 2016)

Table PG1. Range of Alpha1-Antitrypsin Serum Levels by Common Phenotypes

	MM	MZ	SS	SZ	ZZ	Znull	Null-Null
mmol	20-48	17-33	15-33	8-16	2.5-7	<2.5	0
mg/dL	150-350	90-210	100-200	75-120	20-45	<20	0

Exclusions:

Genetic testing for alpha₁-antitrypsin deficiency is considered experimental/investigational for all other indications.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

81332

Other codes (investigational, not medically necessary, etc.):

N/A

Note: Code(s) may not be covered by all contracts or certificates. Please consult customer or provider inquiry resources at BCBSM or BCN to verify coverage.

Rationale

GENETIC TESTING OF INDIVIDUALS WITH SUSPECTED ALPHA₁-ANTITRYPSIN DEFICIENCY

Clinical Context and Test Purpose

Genetic testing may be used in situations when alpha₁-antitrypsin deficiency (AATD) is suspected by clinical presentation but not confirmed by serum testing. The purpose of genetic testing is to rule in AATD and determine the genotype. Genetic testing may also be used when AATD is confirmed by serum testing to determine the genotype. The genotype has prognostic implications that will determine management strategies for both pulmonary and extrapulmonary manifestations.

The following PICO's were used to select literature to inform this review.

Populations

The intended populations of interest is individuals with suspected AATD determined using the following criteria.(1)

- Clinical factors:
 - Individuals with chronic obstructive pulmonary disease (COPD);
 - Individuals with asthma and airflow obstruction not completely reversible with bronchodilators;
 - Individuals with otherwise unexplained liver disease;
 - Individuals with necrotizing panniculitis;
 - Individuals with anti-proteinase 3-positive vasculitis (cytoplasmic anti-neutrophil cytoplasmic antibody-positive vasculitis);
 - Individuals with bronchiectasis without evident etiology.
- Family history:
 - A first-degree relative is defined as a parent, child, or sibling.

Interventions

The intervention of interest is genetic testing for AATD.

Comparators

The following test is currently being used to make decisions about managing AATD: standard care without genetic testing.

Outcomes

Beneficial outcomes resulting from a true positive test result are monitoring for multisystem complications, initiation of accepted therapies and potentially behavioral changes (e.g., smoking cessation). Harmful outcomes resulting from a false-positive test result are

unnecessary monitoring or treatment. Harmful outcomes resulting from a false-negative test result are a delay in detection of liver complications.

The time period of interest for measuring outcomes is years.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess the clinical validity of genetic testing for AATD in individuals with suspected AATD, studies should report sensitivity, specificity, positive and negative predictive values. Additionally, studies reporting false positive rates and false negative rates are informative.
- To assess the clinical utility of genetic testing for AATD in individuals with suspected AATD, studies should demonstrate how results of the genetic tests impacted treatment decisions and overall management of the individual.

Review of Evidence

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

The U.S. Food and Drug Administration (FDA) decision summary for the Hydragel phenotyping test included some data on clinical sensitivity and specificity.(9) Samples were evaluated from 64 patients with the following diagnoses: congenital alpha₁-antitrypsin deficiency (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 100% (39/39) and the specificity was 92% (23/25). (Note that this analysis excludes 4 individuals with indeterminate diagnoses.)

Several studies have reported on findings of genotyping and/or phenotyping tests in patients with suspected AATD. Greulich et al (2017) reported on genetic testing results for patients in central-eastern Europe suspected of having severe AATD.(10) The alpha₁-antitrypsin (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=1404) 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, 3 (<0.5%) were PiM, 2 (<0.5%) were PiZ, and 2 (<0.5%) were Pi(null)(null).

Sorroche et al (2015) conducted a cross-sectional study of 1002 patients with chronic obstructive pulmonary disorder (COPD).(11) Serum levels of AAT were obtained and, for patients found to have low serum AAT (≤ 100 mg/dL), genotyping using real-time polymerase chain reaction (PCR) was performed. 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 4 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 phenotyping.

Lujic et al (2018) in Serbia published findings of a study with 27 emphysema patients.(12) 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 4 patients found to have 1 or 2 Z alleles. However, genotyping found 2 unusual pathogenic variants and, in both cases, phenotyping found normal variants. Another study by the Serbian research group, published in 2014, performed genotyping using direct sequencing in 50 patients diagnosed with COPD before the age of 45 years.(13) The authors found that genotyping did not identify more AATD patients than using AAT concentrations alone.

Lopez-Campos et al (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.(14) 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%).

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if individuals receive correct therapy, or more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

The proposed clinical utility for genetic testing for AATD is in making the diagnosis of AATD. No direct evidence demonstrating improved outcomes with genetic testing was identified. A chain of evidence can be constructed to support utility.

Chain of Evidence

For an individual with suspected AATD (i.e., due to early-onset emphysema or a family history of emphysema), making a diagnosis of AATD is well-accepted standard of care. In some cases, AATD may be diagnosed based on a clearly abnormal AAT level, but in intermediate cases, the genotype test may confirm the diagnosis.

There is potential that a confirmed diagnosis of AAT may lead to improved respiratory management. Patient knowledge of AAT status could lead to behavioral change that improves health outcomes. In particular, asymptomatic smokers could quit smoking, which prevents or delays onset of lung disease, and symptomatic smokers could quit smoking, which might 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.(15)

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. However, there

are well-established management guidelines from the American Thoracic Society (ATS) and the European Respiratory Society (ERS) for emphysema management in AATD. In addition, the intensity and/or timing of other treatments may differ for patients with known AATD. This includes antibiotic treatments for lung infections and vaccinations (influenza, pneumococcus, hepatitis A and B).(1)

Because of the multisystem nature of AATD, monitoring for hepatic involvement is also indicated.

Smoking Cessation

American Thoracic Society (ATS) and the European Respiratory Society (ERS) (2003) published a joint statement on diagnosis and management of AATD.(1) The joint statement was based on systematic reviews and an evidence-based approach to evaluating evidence. A review of smoking cessation studies in the joint statement did not identify any randomized controlled trials (RCTs) on the impact of AATD status on smoking cessation. However, ATS and ERS identified an RCT on a related topic. This 1997 trial found that, at one year, patients 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; quit rates did not differ significantly between the two groups.(16)

Carpenter et al (2007) reported on findings of a survey of volunteers for genetic testing for AATD.(17) A total of 4344 individuals completed a test kit; 331 (7.6%) respondents were rejected because their blood samples were insufficient. The remaining participants were mailed a follow-up letter with test results and a genotype-specific brochure. Results of the testing revealed that 2228 (56%) of the valid samples tested normal, 1530 (38%) were found to be heterozygous carriers for AATD (MZ genotype), and 255 (6%) were found to be severely AATD (SZ or ZZ genotype). A total of 729 (33%) of 2228 participants with valid blood samples identified themselves as current cigarette smokers. These smokers were sent an additional questionnaire 3 months after the initial letter. Test results among smokers were 55% normal genotype, 38% carrier, and 7% severely AATD. Of the 729 surveys sent to smokers, 205 (28%) were completed. Six smokers were excluded because they smoked fewer than 6 cigarettes per day, leaving 199 participants in the study sample. Survey responders were more likely to be older than non-responders; 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 individuals with a normal genotype (59% vs 33%, $p < 0.05$). Of 8 quit behaviors listed in the survey, AATD smokers reported engaging in a mean (SD) of 2.4 (2.3) attempts. This was significantly higher than the number of quit behaviors reported by carriers (0.7, $SD = 1.3$) or individuals with a normal genotype (1.3, $SD = 2.0$; $p = 0.04$). There was no significant difference between groups, however, in the abstinence rate at 3 months (defined as 24-hour point prevalence).

Ashenurst et al (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).(18) 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; $p < .0015$) and individuals with homozygous Z variants were more likely to report a decrease in alcohol consumption (odds ratio, 3.9; $p < .0015$) than individuals without Z variants.

Smoking Prevention

The ATS and ERS joint statement on AATD identified two case-control studies that included children identified at birth as having AATD and matched to a demographically similar control group. The number of children with AATD was 61 in 1 study and 22 in the other. These studies reported a lower frequency of adolescent smoking in individuals identified at birth as having AATD compared with the control individuals.(1)

Treatments for Alpha₁-Antitrypsin Deficiency

Alteration of Timing or Intensity of Treatments for Patients with Alpha₁-Antitrypsin Deficiency

The ATS and ERS joint statement on AATD recommended the following interventions for patients with emphysema who have AATD:(1)

- Inhaled bronchodilators
- Preventive vaccinations against influenza and pneumococcus
- Supplemental oxygen when indicated by conventional criteria, including during air travel
- Pulmonary rehabilitation for individuals with functional impairment
- Consideration of lung transplantation for selected individuals with severe functional impairment and airflow obstruction
- Early antibiotic treatment for individuals with purulent acute exacerbations of chronic obstructive pulmonary disease (COPD).

Authors noted that these are general recommendations for treating patients with COPD and are also applicable to those with pulmonary disease not associated with AATD; no controlled studies specific to AATD were cited in support of the previous 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 also 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."(8)

Alpha₁-Antitrypsin Augmentation Therapy

A 2016 Cochrane review addressed the benefits and harms of AAT augmentation therapy in individuals with AATD and lung disease.(19) 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 3 studies did not find a significant difference in forced expiratory volume in 1 second (FEV₁) deterioration over the course of the studies in the treatment compared with the placebo group. The pooled standardized mean difference (SMD) in FEV₁ 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 computed tomography 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 on the impact of AAT augmentation therapy on health outcomes.

The RCTs included in the Cochrane review are described next. Two of the 3 RCTs were conducted by the same research team, Dirksen et al.(20,21) The first trial, published in 1999, enrolled 56 ex-smokers with AATD (ZZ phenotype verified by isoelectric focusing) and FEV₁ of 30% to 80% of the predicted normal value. Patients were treated with augmentation therapy or placebo for 3 years. The primary outcome (decline in FEV₁) did not differ significantly between groups at follow-up. The second trial, published in 2009, included 77 ex-smokers or never smokers with AATD defined as AAT serum concentrations less than 11 µM. Patients were treated for 2 years with augmentation therapy or placebo. The primary outcome was lung density measured by computed tomography (CT) scans. Lung density decline was reported in 4 ways (2 methods of adjustment for lung variability and 2 statistical methods). One of the 4 lung density outcome variables found a statistically significant between-group difference at follow-up (p=0.049) and the other 3 had marginally significant findings (p=0.59 to p=0.084). Decrease in FEV₁, reported as a secondary outcome, did not differ significantly between groups.

The third RCT was published by Chapman et al (2015).(22) It was a double-blind placebo-controlled study in patients with emphysema secondary to AATD and FEV₁ of 35% to 70% of the predicted normal value. AATD was defined as AAT serum levels or 11 µM or less. Patients were treated with augmentation therapy or placebo for 2 years. The primary outcome was the annual rate of decrease in lung density. Lung density values were calculated at both the total lung capacity (TLC) and functional residual capacity (FRC). When measured at TLC and FRC combined, the relative reduction in lung density in the augmentation versus the placebo group was 29% (95% CI, 0.93% to 76.4%) and this difference was not statistically significant. When measured separately, there was a significantly greater decrease in lung density at TLC alone in the augmentation (-1.5 standard error: 0.2, g/L per year) versus placebo (-2.2 standard error: 0.3, g/L per year) group and no significant difference between groups in lung density at FRC alone. Change in FEV₁, a secondary outcome, did not differ significantly between groups but the authors noted that the study was not powered for this outcome.

Section Summary: Genetic Testing of Individuals With Suspected Alpha1-Antitrypsin Deficiency

No direct evidence was identified to demonstrate clinical utility. A chain of evidence suggests that making a diagnosis of AATD in individuals with suspected AATD can support clinical utility. There are preventive measures such as smoking avoidance, smoking cessation, use of inhaled bronchodilators, and vaccinations that may be recommended when an AATD diagnosis is confirmed. Additional patient management decisions influenced by a confirmed diagnosis may include optimizing current treatments and continued monitoring for disease progression.

A U.S. national guideline has recommended interventions for individuals with emphysema found to have AATD (e.g., preventive vaccinations, early antibiotic treatment). Monitoring for hepatic involvement is also indicated.

The only AATD-specific treatment is AAT augmentation therapy, which is often prescribed for patients with documented AATD and emphysema. A Cochrane review concluded that the RCT evidence was insufficient to determine whether AAT augmentation therapy is effective for

improving health outcomes in patients with AATD. In the pooled analysis of data from 3 studies, there was significantly greater decrease in lung density among patients who received augmentation therapy; the differences in FEV₁ deterioration and carbon monoxide diffusion were not statistically significant. In individual RCTs, lung density outcomes varied and none found a statistically significant benefit of augmentation therapy on FEV₁ decline.

SUMMARY OF EVIDENCE

For individuals who have suspected alpha₁-antitrypsin deficiency (AATD) who receive genetic testing for AATD, the evidence includes studies on analytic and clinical validity, and several controlled studies assessing potential clinical utility. Relevant outcomes are test accuracy and validity, symptoms, and morbid events. Genetic testing can confirm a diagnosis of AATD, suggested by serum testing, by identifying the known genetic variants associated with the disease and identify AATD when a diagnosis is uncertain due to suspicious clinical presentation that is not confirmed by serum testing. A chain of evidence suggests that making a diagnosis of AATD in individuals with suspected AATD can support clinical utility by allowing monitoring for multisystem complications and initiation of accepted therapies. Knowledge of AATD status may lead to behavior changes or changes in medical management that lead to improved health outcomes; however, there is limited supportive evidence. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Supplemental Information

PRACTICE GUIDELINES AND POSITION STATEMENTS

Alpha-1 Foundation

In 2016, the Alpha-1 Foundation made the following recommendations for AATD testing:⁸

- "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 European Respiratory Society

In 2003, the American Thoracic Society published recommendations on the diagnosis and management of individuals with AATD.(1) Table 1 summarizes the relevant recommendations.

Table 1. Recommendations for Diagnosis and Management of AATD

Recommendations for Diagnostic Testing	GOR ^a
<ul style="list-style-type: none"> · “Symptomatic adults with emphysema, chronic obstructive pulmonary disease (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 AAT deficiency” 	A
<ul style="list-style-type: none"> · “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” 	B
<ul style="list-style-type: none"> · “Adults with asthma in whom airflow obstruction is completely reversible · “Predispositional testing” · “Population screening of smokers with normal spirometry” 	C
<ul style="list-style-type: none"> · “Predispositional fetal testing” · “Population screening of either neonates, adolescents, or adults”^b 	D

AAT: alpha₁-antitrypsin; AATD: alpha₁-antitrypsin deficiency; C-ANCA: cytoplasmic anti-neutrophil cytoplasmic antibodies; COPD: chronic obstructive pulmonary disease; GOR grade of recommendation.

^a 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).

^b Population screening is not recommended currently. However, a possible exception (type B recommendation) may apply in countries satisfying all three of the following conditions: (1) the prevalence of AAT deficiency is high (about 1/1500, or more); (2) smoking is prevalent; and (3) adequate counseling services are available.

Canadian Thoracic Society

In 2012, the Canadian Thoracic Society published a clinical practice guideline on alpha₁-antitrypsin deficiency (AATD) testing and alpha₁-antitrypsin (AAT) augmentation therapy.(23)

The recommendations for targeted testing for AATD include:

- Targeted testing for AATD may be considered in those individuals with COPD who were either diagnosed before 65 years of age or who had less than a 20 pack-year history of smoking.
- Targeted testing for AATD was not recommended in individuals with bronchiectasis or asthma.

European Respiratory Society

In 2017, the European Respiratory Society published an updated statement on the diagnosis and treatment of pulmonary disease with AATD.(24) Statements relating to genetic testing include:

- Quantitative determination of AAT levels is the crucial first step in identifying AATD, which must be supported by qualitative tests to identify the genetic mutation(s) causing AATD.

- Protein phenotyping by isoelectric focusing identifies variants where AAT is present, including the rare variants F, I, and P etc.
- Genotyping allows a rapid and precise identification/exclusion of S and Z alleles and other variants, where specific primers are available.
- Gene sequencing remains necessary for cases where a null variant or a deficient variant other than Z or S is suspected.
- Testing of relatives of identified patients should be considered after appropriate counseling.

World Health Organization

A 1997 memorandum was published by the World Health Organization following a 1996 meeting on AATD, included the following recommendations relevant to this review:(25)

- “[A]ll patients with COPD and adults and adolescents with asthma [should] be screened once for AAT deficiency using a quantitative test. Those with abnormal results on screening should undergo PI [protease inhibitor] typing.
- “[N]eonatal AAT screening programmes should be undertaken in all developed countries with Caucasian populations.” Among research needs listed is an “Analysis of the costs and benefits of screening, as a prelude to implementing neonatal screening for AAT deficiency.”
- “There is an urgent need for randomized clinical trials of the efficacy of AAT augmentation therapy in persons with the deficiency.”

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATION

Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently ongoing trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01983241 ^a	A Randomized, Double-Blind, Placebo Controlled Study to Assess the Efficacy and Safety of Two Dose Regimens (60 mg/kg and 120 mg/kg) of Weekly Intravenous Alpha ₁ Protease Inhibitor (Human) in Subjects With Pulmonary Emphysema Duetto Alpha ₁ Antitrypsin Deficiency	345	Jul 2026
NCT00500123	Alpha ₁ Coded Testing(ACT) Study	50,000	Jan 2050

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

Government Regulations

National:

There is no National Coverage Determination for this genetic test.

Local:

There is no Local Coverage Determination for this genetic test.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

N/A

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 5/24/24, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
11/1/14	8/19/14	8/28/14	Joint policy established
1/1/16	10/13/15	10/27/15	Routine maintenance
1/1/17	10/11/16	10/11/16	Routine maintenance
1/1/18	10/19/17	10/19/17	Routine maintenance References and rationale updated Added local coverage information for Medicare
1/1/19	10/16/18	10/16/18	Routine maintenance
1/1/20	10/15/19		Routine maintenance
11/1/20	8/18/20		Routine maintenance
11/1/21	8/17/21		Routine maintenance
11/1/22	8/16/22		Routine maintenance
11/1/23	8/15/23		Routine maintenance (slp) Vendor Managed: Avalon
11/1/24	8/20/24		Routine maintenance (slp) Vendor Managed: Avalon

Next Review Date: 3rd Qtr, 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING FOR ALPHA₁-ANTITRYPSIN DEFICIENCY

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered, criteria apply
BCNA (Medicare Advantage)	Refer to Medicare information under the Government Regulations section of the policy
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.