Medical Policy
Genetic Testing for Alpha\textsubscript{1}-Antitrypsin Deficiency

**Table of Contents**
- Policy: Commercial
- Policy: Medicare
- Authorization Information
- Coding Information
- Description
- Policy History
- Information Pertaining to All Policies
- References

**Policy Number:** 906
BCBSA Reference Number: 2.04.79
NCD/LCD: NA

**Related Policies**
None

**Policy**
**Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity**

Genetic testing for alpha\textsubscript{1}-antitrypsin deficiency may be considered **MEDICALLY NECESSARY** when both of the following conditions are met:

1. Patient is suspected of having alpha\textsubscript{1} -antitrypsin deficiency because of clinical factors and/or because the patient may be at high risk of having alpha\textsubscript{1} -antitrypsin deficiency due to a first-degree relative with alpha\textsubscript{1}-antitrypsin deficiency; AND
2. Patient has a serum alpha\textsubscript{1} -antitrypsin level in the range of severe deficiency.

Genetic testing for alpha\textsubscript{1} -antitrypsin deficiency is considered **INVESTIGATIONAL** in all other situations.

Table PG1 shows the range of serum levels of alpha\textsubscript{1}-antitrypsin by common phenotypes according to the commercial standard milligram per deciliter and the purified standard micromole. A level less than 11 \textmu mol 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, 2011)

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>MM (\textmu mol)</th>
<th>MZ (\textmu mol)</th>
<th>SS (\textmu mol)</th>
<th>SZ (\textmu mol)</th>
<th>ZZ (\textmu mol)</th>
<th>Znull (\textmu mol)</th>
<th>Null-Null (\textmu mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>\textmu mol</strong></td>
<td>20-48</td>
<td>17-33</td>
<td>15-33</td>
<td>8-16</td>
<td>2.5-7</td>
<td>&lt;2.5</td>
<td>0</td>
</tr>
<tr>
<td><strong>mg/dL</strong></td>
<td>150-350</td>
<td>90-210</td>
<td>00-200</td>
<td>75-120</td>
<td>20-45</td>
<td>&lt;20</td>
<td>0</td>
</tr>
</tbody>
</table>
Medicare HMO Blue℠ and Medicare PPO Blue℠ Members

Medical necessity criteria and coding guidance for Medicare Advantage members living in Massachusetts can be found through the link below.

Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)

For medical necessity criteria and coding guidance for Medicare Advantage members living outside of Massachusetts, please see the Centers for Medicare and Medicaid Services website for information regarding your specific jurisdiction at https://www.cms.gov.

Prior Authorization Information

Pre-service approval is required for all inpatient services for all products. See below for situations where prior authorization may be required or may not be required for outpatient services.

Yes indicates that prior authorization is required.
No indicates that prior authorization is not required.
N/A indicates that this service is primarily performed in an inpatient setting.

<table>
<thead>
<tr>
<th>Outpatient</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial Managed Care (HMO and POS)</td>
<td>No</td>
</tr>
<tr>
<td>Commercial PPO and Indemnity</td>
<td>No</td>
</tr>
<tr>
<td>Medicare HMO Blue℠</td>
<td>No</td>
</tr>
<tr>
<td>Medicare PPO Blue℠</td>
<td>No</td>
</tr>
</tbody>
</table>

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

CPT Codes

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81332</td>
<td>SERIPINA 1 (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)</td>
</tr>
</tbody>
</table>

ICD-9 Diagnosis Codes

<table>
<thead>
<tr>
<th>ICD-9-CM diagnosis codes:</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>273.4</td>
<td>Alpha-1 antitrypsin deficiency</td>
</tr>
</tbody>
</table>

ICD-10 Diagnosis Codes

<table>
<thead>
<tr>
<th>ICD-10-CM diagnosis codes:</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>E88.01</td>
<td>Alpha-1-antitrypsin deficiency</td>
</tr>
</tbody>
</table>
**Description**

**DESCRIPTION OF DISEASE**

Alpha1-antitrypsin deficiency (AATD) is an autosomal recessive genetic disorder that decreases production of the alpha1-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 the United States to be between 1 in 2857 and 1 in 5097 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.

**AATD 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 (ie, 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 mutations 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 (ie, between ages 40 and 50 years) in individuals with AATD 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 mutations.\(^1\) In addition, individuals with AATD are advised to avoid other substances that can irritate the lungs (eg, cigarette smoke, dust, workplace chemicals), as well as substances that can cause liver damage (eg, 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 AAT
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 mutation.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 mutations (ie, 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.

Summary
Alpha1-antitrypsin deficiency (AATD) is an autosomal recessive genetic disorder that decreases production of the alpha1-antitrypsin (AAT) protein or production of abnormal types of the protein that are functionally deficient. Individuals with AATD, especially smokers, have an increased risk of lung and liver disease. Available tests measure serum AAT levels and phenotype AAT protein variants. Genetic testing is also available to detect the most common mutations associated with AATD.

For individuals who have suspected 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. In some cases, genetic testing only confirms a diagnosis of AATD by identifying the known genetic variants associated with the disease. More importantly, genetic testing can identify AATD when a diagnosis is uncertain. 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.

The available studies suggest that knowledge of AATD status may lead to more quit attempts but not higher smoking cessation rates. 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 published evidence suggests that knowledge of AATD status may discourage nonsmokers from initiating smoking and may increase quit attempts among smokers, but it has not been shown to increase successful quitting. A Cochrane systematic review of 3 randomized controlled trials on AAT augmentation therapy had mixed findings; change in lung density, but not other outcomes, improved with
treatment. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

As reflected by clinical guidelines, it is generally accepted clinically that knowledge of AATD status could lead to behavioral change and change in treatment that could lead to an improvement in health outcomes and that genetic testing to confirm a diagnosis of AATD is a reasonable clinical practice. Thus, genetic testing of individuals with suspected AATD and serum AT level in the range of severe deficiency may be considered medically necessary.

### Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>4/2017</td>
<td>BCBSA National policy review. Summary clarified. New references added. 4/1/2017</td>
</tr>
<tr>
<td>2/2017</td>
<td>New references added from BCBSA National medical policy.</td>
</tr>
<tr>
<td>6/2015</td>
<td>New references added from BCBSA National medical policy.</td>
</tr>
<tr>
<td>7/2014</td>
<td>New references added from BCBSA National medical policy.</td>
</tr>
<tr>
<td>6/2014</td>
<td>Updated Coding section with ICD10 procedure and diagnosis codes, effective 10/2015.</td>
</tr>
<tr>
<td>11/2013</td>
<td>Corrected CPT code: Correct code is 81332 not 81322.</td>
</tr>
<tr>
<td>5/2013</td>
<td>New references from BCBSA National medical policy.</td>
</tr>
<tr>
<td>2/2013</td>
<td>New policy describing coverage and non-coverage.</td>
</tr>
</tbody>
</table>

### Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:
- **Medical Policy Terms of Use**
- **Managed Care Guidelines**
- **Indemnity/PPO Guidelines**
- **Clinical Exception Process**
- **Medical Technology Assessment Guidelines**

### References


