

(20479)

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**Preauthorization is required.**

*The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.*

Populations	Interventions	Comparators	Outcomes
Individuals: • With suspected alpha <sub>1</sub> -antitrypsin deficiency	Interventions of interest are: • Genetic testing for alpha <sub>1</sub> -antitrypsin deficiency	Comparators of interest are: • Standard care without genetic testing	Relevant outcomes include: • Test validity • Symptoms • Morbid events

### DESCRIPTION

Alpha<sub>1</sub>-antitrypsin deficiency (AATD) is an autosomal recessive genetic disorder that results in decreased production of functional alpha<sub>1</sub>-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 pathogenic variants associated with AATD.

### SUMMARY OF EVIDENCE

For individuals who have suspected AATD who receive genetic testing for AATD, the evidence includes studies on 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 the 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.

As reflected by clinical guidelines, it is generally accepted that knowledge of AATD status could lead to behavioral change and change in treatment that can 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 AAT level in the range of severe deficiency may be considered medically necessary.

**POLICY**

Genetic testing for alpha<sub>1</sub>-antitrypsin deficiency may be considered **medically necessary** when either of the following conditions are met:

1. Patient is suspected of having alpha<sub>1</sub>-antitrypsin deficiency because of clinical factors and/or because the patient may be at high risk of having alpha<sub>1</sub>-antitrypsin deficiency due to a first-degree relative with alpha<sub>1</sub>-antitrypsin deficiency (see Policy Guidelines); OR
2. Patient has a serum alpha<sub>1</sub>-antitrypsin level in the range of severe deficiency (see Policy Guidelines).

Genetic testing for alpha<sub>1</sub>-antitrypsin deficiency is considered **investigational** in all other situations.

**POLICY GUIDELINES**

According to the 2003 joint statement on diagnosis and management of AATD by the American Thoracic Society/ European Respiratory Society, the following features should prompt suspicion by physicians that their patient may be more likely to have AATD:

**CLINICAL FACTORS**

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

**FAMILY HISTORY**

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

AATD occurs predominantly in whites. For example, the prevalence in Sweden is approximately one in 1,575; the estimated prevalence in the United States is between one in 2,857 and one in 5,097 (American Thoracic Society & European Respiratory Society, 2003).

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

Range of Alpha<sub>1</sub>-Antitrypsin Serum Levels by Common Phenotypes

	<b>MM</b>	<b>MZ</b>	<b>SS</b>	<b>SZ</b>	<b>ZZ</b>	<b>Znull</b>	<b>Null-Null</b>
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

**GENETICS NOMENCLATURE UPDATE**

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical pro-

protocol updates starting in 2017 (see Table PG2). The Society's nomenclature is recommended by the Human Genome Project, the HUMAN Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG3 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG2. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG3. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

## GENETIC COUNSELING

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

## MEDICARE ADVANTAGE

For Medicare Advantage genetic testing for alpha<sub>1</sub>-antitrypsin deficiency is considered **medically necessary** for patients who have antitrypsin deficiency to guide therapeutic decision-making.

## BACKGROUND

### ALPHA<sub>1</sub>-ANTITRYPSIN DEFICIENCY

Alpha<sub>1</sub>-antitrypsin deficiency (AATD) is an autosomal recessive genetic disorder that decreases the production of functional alpha<sub>1</sub>-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 one in 2857 and one in 5097 individuals.<sup>1</sup>

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 (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) and have mean serum AAT concentrations ranging from 20 to 53  $\mu\text{mol/L}$ . The most common abnormal forms are the Z and the S alleles. Individuals with two copies of the Z allele (ZZ) tend to be most severely affected, with mean serum AAT concentrations of 2.5 to 7  $\mu\text{mol/L}$  and a high risk of chronic obstructive pulmonary disease. Individuals with genotype SS and heterozygous individuals with genotype MZ have a low risk of chronic obstructive pulmonary disease 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.<sup>2</sup>

#### 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 AATD who smoke cigarettes and/or are exposed to occupational dust or fumes. In nonsmokers and individuals without environmental exposure, the 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 a liver transplant in newborns. In a large series (1976) of 127 newborns with AATD found by screening, the prevalence of liver damage was 11%, severe in about two-thirds of cases.<sup>3</sup>

#### 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.<sup>4</sup>

#### 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.<sup>1</sup> 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. 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 three to four 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.<sup>5,6</sup>

Other aspects of AATD management 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 pathogenic variant.<sup>7</sup>

The alpha<sub>1</sub> 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 alpha<sub>1</sub> 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 through the 510(k) process for the qualitative detection and identification of the phenotypes of AAT protein. Food and Drug Administration product code: OBZ.

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the Food and Drug Administration has chosen not to require any regulatory review of this test.

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Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

**REFERENCES**

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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23. National Government Services, Inc. (Primary Geographic Jurisdiction 06 & K - Illinois, Minnesota, Wisconsin, Connecticut, New York - Entire State, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont) Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000), Revision Effective Date for services performed on or after 01/01/2019.