

MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR ALPHA1- ANTITRYPSIN DEFICIENCY
POLICY NUMBER	MP 2.251

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☐ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☒ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	RETIRED 7/1/2026

[POLICY RATIONALE](#)
[CODING INFORMATION](#)

[PRODUCT VARIATIONS](#)
[DEFINITIONS](#)
[REFERENCES](#)

[DESCRIPTION/BACKGROUND](#)
[DISCLAIMER](#)
[POLICY HISTORY](#)

I. POLICY

Genetic testing for alpha1-antitrypsin (AAT) deficiency may be considered **medically necessary** when either of the following conditions are met:

1. Individual is suspected of having alpha1-antitrypsin deficiency because of clinical factors and/or because the individual may be at high risk of having alpha1-antitrypsin deficiency due to a first-degree relative with AAT deficiency (see Policy Guidelines); **or**
2. Individual has a serum alpha₁-antitrypsin level in the range of severe deficiency (see Policy Guidelines).

Genetic testing for alpha₁-antitrypsin deficiency is considered **investigational** in all other situations. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this testing.

Policy Guidelines

Clinical factors relevant for suspicion of alpha1-antitrypsin deficiency based on 2016 Alpha-1 Foundation clinical practice guidelines are:

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.

MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR ALPHA1- ANTITRYPSIN DEFICIENCY
POLICY NUMBER	MP 2.251

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 mmol 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, 2024).

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

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 evidence review updates starting in 2017 (see Table PG2). The Society's nomenclature is recommended by the Human Variome 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

MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR ALPHA1- ANTITRYPSIN DEFICIENCY
POLICY NUMBER	MP 2.251

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

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

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.

II. PRODUCT VARIATIONS

[TOP](#)

This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations. Please see additional information below.

FEP PPO: Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at:

<https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies>

III. DESCRIPTION/BACKGROUND

[TOP](#)

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 2857 and 1 in 5097 individuals.

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

MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR ALPHA1- ANTITRYPSIN DEFICIENCY
POLICY NUMBER	MP 2.251

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 $\mu\text{mol/L}$. 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 $\mu\text{mol/L}$ 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.

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.

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.

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. 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 3 to 4 weeks for life. Inhaled AAT

MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR ALPHA1- ANTITRYPSIN DEFICIENCY
POLICY NUMBER	MP 2.251

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.

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.

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 AAT 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 must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the FDA has chosen not to require any regulatory review of this test.

MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR ALPHA1- ANTITRYPSIN DEFICIENCY
POLICY NUMBER	MP 2.251

IV. RATIONALE

[TOP](#)

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.

V. DEFINITIONS

N/A

[TOP](#)

VI. DISCLAIMER

[TOP](#)

Capital Blue Cross' medical policies are used to determine coverage for specific medical technologies, procedures, equipment, and services. These medical policies do not constitute medical advice and are subject to change as required by law or applicable clinical evidence from independent treatment guidelines. Treating providers are solely responsible for medical advice and treatment of members. These policies are not a guarantee of coverage or payment. Payment of claims is subject to a determination regarding the member's benefit program and eligibility on the date of service, and a determination that the services are medically necessary and appropriate. Final processing of a claim is based upon the terms of contract that applies to the members' benefit program, including benefit limitations and exclusions. If a provider or a member has a question concerning this medical policy, please contact Capital Blue Cross' Provider Services or Member Services.

VII. CODING INFORMATION

[TOP](#)

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

Procedure Codes								
G0452	81332							

MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR ALPHA1- ANTITRYPSIN DEFICIENCY
POLICY NUMBER	MP 2.251

ICD-10-CM Diagnosis Code	Description
E88.01	Alpha1-antitrypsin deficiency

VIII. REFERENCES

[TOP](#)

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MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR ALPHA1- ANTITRYPSIN DEFICIENCY
POLICY NUMBER	MP 2.251

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IX. POLICY HISTORY

[TOP](#)

MP 2.251	04/06/2020 Minor Review. Policy statement changed to now state “either” and “or” vs “both” and “and”. References updated.
	01/29/2021 Consensus Review. No change to policy statement. References and coding review.
	06/16/2022 Consensus Review. No change to policy statement. References updated. Coding reviewed.
	01/05/2023 Consensus Review. No change to policy statement. References reviewed and updated.
	02/19/2024 Consensus Review. Updated statement, guidelines, and background regulatory status. No change in intent. References reviewed and updated. No change to coding.

MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR ALPHA1- ANTITRYPSIN DEFICIENCY
POLICY NUMBER	MP 2.251

	02/10/2025 Consensus Review. No change to policy statement. References updated. Coding reviewed.
	07/22/2025 Administrative Update. Removed Benefit Variations Section and updated Disclaimer.
	01/02/2026 Consensus Review. No changes to policy statement. Updated product variations and references. No coding changes.
	02/10/2026 Retirement Review. Evicore delegation.

[Top](#)

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