# Alpha-1-Antitrypsin deficiency genetic testing
**(Serpina 1 gene)**

**Date of Origin: 4/1/2019** **Last Review Date: 4/24/2024** **Effective Date: 5/1/2024**

**Dates Reviewed: 4/22/2020, 4/2021, 3/2022, 4/2023, 4/2024**

**Developed By:** Medical Necessity Criteria Committee

## I. Description

Alpha-1-antitrypsin (A1A) is a protein that inhibits other enzymes such as neutrophil elastase from degrading protein components of the alveolar walls of the lung. It is a serine protease inhibitor predominantly synthesized in the liver and secreted into bloodstream. The inhibition function is especially important in the lungs because it protects against excess tissue degradation. Tissue degradation due to A1A deficiency is associated with an increased risk for early onset panlobular emphysema.
The SERPINA 1 gene provides instructions for making a protein called alpha-1 antitrypsin, which is a type of serine protease inhibitor (serpin). Serpins help control several types of chemical reactions by blocking (inhibiting) the activity of certain enzymes.

Alpha-1-antitrypsin deficiency (AATD) is an inherited metabolic disorder affecting the lungs, liver, and rarely skin. It 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. AATD results from mutations in the SERPINA1 gene, which codes for the enzyme alpha-1 antitrypsin (AAT). In particular, AATD has been associated with the development of chronic obstructive pulmonary disease (COPD), characterized by permanent destruction of the alveolar distal unit of the terminal bronchioles (emphysema) and increased risk for infectious exacerbations.

Pulmonary manifestations

In the lungs, the most common manifestation is early-onset (patients in their 30s and 40s) panacinar emphysema most pronounced in the lung bases. The natural history of lung damage progression in severe AATD individuals is impacted significantly by smoking. Smoking appears to hasten development of emphysema by 10 to 15 years. These individuals should be monitored closely for lung and liver function. In non-smokers and individuals without environmental exposure, the onset occurs more commonly in the sixth decade. Childhood –onset lung disease is rare with AATD. AATD causes chronic obstructive pulmonary disease (i.e., emphysema and bronchiectasis).

Liver manifestations

AATD is also associated with liver disease, thought to occur due to toxic gain-of-function, leading to an aggregation of damaged AAT in the liver cells. Liver disease in older children and adults with signs of

established cirrhosis, including variceal hemorrhage or ascites. Affected infants may present in the newborn period with cholestatic jaundice, at times acholic stools and hepatomegaly

Skin manifestations

Necrotizing panniculitis is a rare, but well recognized complication of AAT deficiency. This condition is characterized by inflammatory and necrotizing lesions of the skin and subcutaneous tissue.

The alpha-1 antitrypsin protein level should be the first line test for a suspected diagnosis of AAT deficiency in symptomatic individuals with unexplained liver disease or obstructive lung disease that is not asthma or in a middle age individual with unexplained dyspnea.

## II. Criteria: CWQI HCS-0252

A. Moda will provide coverage for genetic testing for alpha-1 antitrypsin deficiency when it is determined to be medically necessary when **ALL** the medical criteria and guidelines as follows are met:
    a. Patient is suspected of having alpha-1 antitrypsin deficiency as a result of clinical factors and/or because the patient may be at high risk of having alpha-1 antitrypsin deficiency due to a first degree relative with AAT deficiency;
        i. Clinical factors may include **1 or more** of the following:
            1. Early onset emphysema (age of 45 years or less)
            2. Emphysema in the absence of a recognized risk factor (smoking, occupational dust or chemical fumes exposure etc.)
            3. Emphysema, and X-rays show less density in the lungs than normal (prominent basilar hyperlucency)
            4. Individuals with unexplained liver disease, including neonates, children, and adults, particularly the elderly
            5. Family history of any of the following; emphysema, bronchiectasis, liver disease, or inflammation of the fat under the skin (necrotizing panniculitis)
            6. Bronchiectasis without an evident cause or etiology
        ii. Family history (first degree relative defined as a parent, child or sibling)

    b. Patient has an abnormally low (less than 120mg/dL) serum alpha-1 antitrypsin level. Confirmatory testing would include either protease inhibitor typing or genetic testing for common mutations.

B. Genetic testing for Alpha-1 deficiency is considered investigational in all other situations

## III. Information Submitted with the Prior Authorization Request:

1. Provider chart notes
2. Family history

## IV. CPT or HCPC codes covered:

| Codes | Description |
|---|---|
| 81332 | SERPINA 1 (serpin peptidase inhibitor, clade A, alpha-1 antiproteinase, antitrypsin, member 1) (eg alpha-1-antitrypsin deficiency), gene analysis, common variants (eg, S and Z) |

## V. CPT or HCPC codes NOT covered:

| Codes | Description |
|---|---|
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## VI. Annual Review History

| Review Date | Revisions | Effective Date |
|---|---|---|
| 4/1/2019 | New criteria | 7/1/2019 |
| 4/22/2020 | Annual review: No changes | 5/1/2020 |
| 4/28/2021 | Annual Review: No changes | 5/1/2021 |
| 3/23/2022 | Annual Review: Title update 'Alpha-1-Antitrypsin deficiency genetic testing' | 4/1/2022 |
| 4/26/2023 | Annual Review: No changes | 5/1/2023 |
| 4/24/2024 | Annual Review: language update-Patient has an abnormally low (less than 120mg/dL) serum alpha-1 antitrypsin level. | 5/1/2024 |

## VII. References


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2. Alpha-1 Antitrypsin Deficiency Testing. Lab Management Guidelines. Retrieved from https://www.evicore.com/-/media/files/evicore/clinical-guidelines/solution/lab-management/healthplan/hne-labpolicybook-v102019_eff01022019_pub12312018.pdf
3. American Thoracic Society/European respiratory society statement standards for the diagnosis and management of individuals with Alpha-1 antitrypsin deficiency, AJRCCM Retrieved from https://www.atsjournals.org/doi/full/10.1164/rccm.168.7.818?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dpubmed
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11. Alpha-1 Antitrypsin Deficiency.https://my.clevelandclinic.org/health/diseases/21175-alpha-1-antitrypsin-deficiency

## Appendix 1 – Applicable Diagnosis Codes:

| Codes | Description |
|---|---|
| E88.01 | Alpha-1-antitrypsin deficiency |
| | |

## Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determination (NCD) and Local Coverage Determinations (LCDs) may exist and compliance with these policies is required where applicable. They can be found at: http://www.cms.gov/medicare-coverage-database/search/advanced-search.aspx. Additional indications may be covered at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD):

| Jurisdiction(s): 5, 8 | NCD/LCD Document (s): |
|---|---|
| | |
| | |

| NCD/LCD Document (s): |
|---|
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| Medicare Part B Administrative Contractor (MAC) Jurisdictions | | |
|---|---|---|
| Jurisdiction | Applicable State/US Territory | Contractor |
| F (2 & 3) | AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ | Noridian Healthcare Solutions, LLC |