

Reimbursement Policy

Testing for Alpha-1 Antitrypsin Deficiency

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I. Policy Description

Alpha 1-antitrypsin deficiency (AATD) is a genetic disease that causes deficient or defective production of the alpha-1 antitrypsin (AAT) protease inhibitor that can affect the lungs, liver, and (rarely) skin.¹ AAT deficiency results in unbalanced rapid breakdown of proteins, especially in the supporting elastic tissue of the lungs.²

II. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the "Applicable State and Federal Regulations" section of this policy document.

- 1) For individuals who are suspected of having alpha-1 antitrypsin (AAT) deficiency, serum quantification of alpha-1 antitrypsin (AAT) protein **and** AAT phenotyping **or** AAT proteotyping (see Note 1) **MEETS COVERAGE CRITERIA** once per lifetime in **any** of the following situations:
 - a) For symptomatic individuals 18 years or older with emphysema, COPD, or asthma.
 - b) For individuals with unexplained liver disease (e.g., chronic hepatitis with or without cirrhosis, chronically elevated aminotransferase levels, portal hypertension, primary liver cancer).
 - c) For individuals with persistent obstruction on pulmonary function tests without identifiable risk factors (e.g., cigarette smoking, occupational exposure).
 - d) For individuals 18 years or older with necrotizing panniculitis.
 - e) For the siblings of an individual with known alpha-1 antitrypsin (AAT) deficiency.
 - f) For individuals with anti-proteinase three-positive vasculitis (C-ANCA [anti-neutrophil cytoplasmic antibody]-positive vasculitis).
 - g) For individuals with bronchiectasis without evident etiology.
 - h) For individuals with neonatal cholestasis.

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- 2) For individuals who have negative genotype results for common variants or who have discordant results between AAT serum levels and proteotype, but for whom a clinical suspicion of AAT deficiency remains, isoelectric focusing/phenotyping **MEETS COVERAGE CRITERIA**.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual's illness.

- 3) For all other situations not described above, testing for AAT deficiency **DOES NOT MEET COVERAGE CRITERIA**.

NOTES:

Note 1: AAT phenotyping should be performed using isoelectric focusing. AAT proteotyping (Pi-typing or protease inhibitor typing) for Z and S alleles should be performed using liquid chromatography-tandem mass spectrometry.

III. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: <http://www.cms.gov/medicare-coverage-database/search.aspx>. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

On November 17, 2017, the FDA approved Grifols' *SERPINA1* Variant Detection System as a qualitative in vitro molecular diagnostic system used to detect variants in *SERPINA1* gene in genomic DNA isolated from human specimens.¹⁰ On November 7, 2019, the FDA approved Grifols' AlphaID™, a cheek swab that can screen patients with COPD for alpha-1 antitrypsin deficiency. It "utilizes an FDA-approved genotyping assay to screen for the 14 most prevalently

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reported genetic mutations associated with Alpha-1, including the S, Z, F, I alleles, as well as rare and null alleles, helping detect patients who are at risk for this treatable condition.”⁴²

On April 6, 2017 the FDA approved the 23andMe PGS Genetic Health Risk Report for Alpha-1 Antitrypsin Deficiency (AATD) which determines if a person has variants associated with a higher risk of developing AATD-associated lung or liver disease. This report is based on a qualitative genetic test for single nucleotide polymorphism detection of the PI*Z (rs28929474) and PI*S (rs17580) variants in the *SERPINA1* gene by using the 23andMe Personal Genome Service.⁴³

IV. Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
82103	Alpha-1-antitrypsin; total
82104	Alpha-1-antitrypsin; phenotype
82542	Column chromatography, includes mass spectrometry, if performed (eg, HPLC, LC, LC/MS, LC/MS-MS, GC, GC/MS-MS, GC/MS, HPLC/MS), non-drug analyte(s) not elsewhere specified, qualitative or quantitative, each specimen
83789	Mass spectrometry and tandem mass spectrometry (eg, MS, MS/MS, MALDI, MS-TOF, QTOF), non-drug analyte(s) not elsewhere specified, qualitative or quantitative, each specimen

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Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

V. Evidence-based Scientific References

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 12. GOLD. Global Strategy for Prevention, Diagnosis, and Management of COPD: 2024 Report. <https://goldcopd.org/2024-gold-report/>
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VI. Revision History

Revision Date	Summary of Changes
09/04/2025	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria.