GENETIC TESTING: LUNG DISORDERS

OVERVIEW

One of the most common forms of inherited lung disorders is alpha-1 antitrypsin deficiency (AATD) 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. Individuals with AATD have an increased risk for lung and liver disease to develop. Genetic testing to diagnose AATD aids in directing proper treatment and identifying at-risk family members.

POLICY REFERENCE TABLE

Below is a list of higher volume tests and the associated laboratories for each coverage criteria section. This list is not all inclusive.

Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
Alpha-1 Antitrypsin Deficiency				
SERPINA1 Known Familial Variant Analysis	SERPINA Targeted Mutation Analysis	81403	E88.01	1, 2, 3, 4
SERPINA1 Common Variant Analysis or Sequencing Analysis	SERPINA1 Common Variant Analysis	81332		
	SERPINA1 Sequencing Analysis	81479		
Other Covered Lung Disorders				
Other Covered Lung Disorders	See list below	81400-81408		5, 6, 7

OTHER RELATED POLICIES

This policy document provides coverage criteria for Genetic Testing for Lung Disorders. Please refer to:

- ***Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay*** for coverage criteria related to diagnostic testing for cystic fibrosis and other multisystem inherited disorders.
- ***Genetic Testing: General Approach to Genetic Testing*** for coverage criteria related to genetic testing for lung disorders and disease that are not specifically discussed in this or another non-general policy.

COVERAGE CRITERIA

ALPHA-1 ANTITRYPSIN DEFICIENCY

SERPINA1 Known Familial Variant Analysis

I. *SERPINA1* targeted variant analysis for a known familial variant (81403) is considered **medically necessary** when:

   A. The member has a close relative with a known pathogenic or likely pathogenic variants in *SERPINA1*.

II. *SERPINA1* targeted variant analysis for a known familial variant (81403) is considered **investigational** for all other indications.

SERPINA1 Common Variant Analysis or Sequencing Analysis

I. *SERPINA1* common variant analysis (81332) or sequencing analysis (81479) to establish a diagnosis of alpha-1 antitrypsin (AAT) deficiency is considered **medically necessary** when:

   A. The member has abnormally low (less than 120mg/dL) or borderline (90-140mg/dL) alpha-1 antitrypsin levels, **AND**

   B. Any of the following:

1. Early-onset emphysema (≤ 45 years)
2. Emphysema in the absence of additional risk factor (e.g., smoking, occupational dust exposure)
3. Emphysema with prominent basilar hyperlucency
4. Otherwise unexplained liver disease
5. Necrotizing panniculitis
6. C-ANCA positive vasculitis (i.e., granulomatosis with polyangiitis)
7. Bronchiectasis without evident etiology
8. A sibling with known AAT deficiency.

II. *SERPINA1* common variant analysis (81332) or sequencing analysis (81479) to establish a diagnosis of alpha-1 antitrypsin deficiency is considered **investigational** for all other indications.

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OTHER COVERED LUNG DISORDERS

The following is a list of conditions that have a known genetic association. Due to their relative rareness, it may be appropriate to cover these genetic tests to establish or confirm a diagnosis.

I. Genetic testing to establish or confirm one of the following genetic lung disorders to guide management is considered **medically necessary** when the member demonstrates clinical features* consistent with the disorder (the list is not meant to be comprehensive, see II below):

   A. Familial Pulmonary Fibrosis
   B. Primary Ciliary Dyskinesia
   C. Pulmonary lymphangioleiomyomatosis (LAM)
   D. Pulmonary alveolar proteinosis (PAP)

II. Genetic testing to establish or confirm the diagnosis of all other lung disorders not specifically discussed within this or another medical policy will be evaluated by the criteria outlined in *General Approach to Genetic Testing* (see policy for coverage criteria).

*Clinical features for a specific disorder may be outlined in resources such as GeneReviews, OMIM, National Library of Medicine, Genetics Home Reference, or other scholarly source.

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NOTES AND DEFINITIONS

1. Close relatives include first, second, and third degree blood relatives:
    a. **First-degree relatives** are parents, siblings, and children
    b. **Second-degree relatives** are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half siblings
    c. **Third-degree relatives** are great grandparents, great aunts, great uncles, great grandchildren, and first cousins

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BACKGROUND AND RATIONALE

Practice Guidelines and Position Statements

American Thoracic Society and European Respiratory Society

The American Thoracic Society and European Respiratory Society published a joint statement on the the diagnosis and management of individuals with alpha-1 antitrypsin deficiency (2003) which stated the following regarding recommendations for diagnostic testing:

Type A Recommendations:

- Symptomatic adults with emphysema, chronic obstructive pulmonary disease (COPD), or asthma with airflow obstruction that is not completely reversible with aggressive treatment with bronchodilators
- Individuals with unexplained liver disease
- Asymptomatic individuals with persistent obstruction on pulmonary function tests with identifiable risk factors (eg, cigarette smoking, occupational exposure)
- Adults with necrotizing panniculitis
- Siblings of an individual with known AAT deficiency

Type B Recommendations:

- Adults with bronchiectasis without evidence etiology
- Adolescents with persistent airflow obstruction
- Asymptomatic individuals with persistent airflow obstruction and no risk factors
- Adults with C-ANCA-positive (anti-proteinase 3-positive) vasculitis
- Individuals with a family history of COPD or liver disease not known to be attributed to AAT deficiency
- Distant relatives of an individual who is homozygous for AAT deficiency
- Offspring or parents of an individual with homozygous AAT deficiency
- Siblings, offspring, parents, or distant relatives of an individual who is heterozygous for AAT deficiency
- Individuals at high risk of having AAT deficiency-related diseases
- Individuals who are not at risk themselves of having AAT deficiency but who are partners of individuals who are homozygous or heterozygous for AAT deficiency

Type C Recommendations:

- Adults with asthma in whom airflow obstruction is completely reversible
- Predispositional testing
- Population screening of smokers with normal spirometry

Type D Recommendations:

- Predispositional fetal testing
- Population screening of either neonates, adolescents, or adults

<u>European Respiratory Society</u>

The European Respiratory Society published an updated statement on the diagnosis and treatment of pulmonary disease in alpha-1 antitrypsin deficiency (2017) that recommends the following related to genetic testing:

- The quantitative determination of AAT levels in blood is a crucial first test to identify AATD. Quantitative deficiency must be supported by qualitative tests to identify the genetic mutation(s) causing AATD.
- Protein phenotyping by isoelectric focusing identifies variants where AAT is present in the sample including the rarer variants F, I and P etc.
- Genotyping allows a rapid and precise identification/exclusion of S and Z alleles and other variants, where specific primers are available.

- Gene sequencing remains necessary for those cases where a null variant or a deficient variant other than Z or S is suspected.
- Testing of relatives of identified patients should be considered after appropriate counselling.
- Genetic testing should be carried out only after informed consent is given and in accordance with the relevant guidelines and legislation.

World Health Organization

The World Health Organization published a memorandum on alpha-1 antitrypsin deficiency (1997) that recommended the following related to genetic testing:

- It is therefore recommended that all patients with COPD and adults and adolescents with asthma be screened once for AAT deficiency using a quantitative test. Those with abnormal results on screening should undergo PI typing.

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REFERENCES

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