GENETIC TESTING: LUNG DISORDERS

OVERVIEW

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

POLICY REFERENCE TABLE

The tests and associated laboratories and CPT codes contained within this document serve only as examples to help users navigate claims and corresponding coverage criteria; as such, they are not comprehensive and are not a guarantee of coverage or non-coverage. Please see the Concert Genetics Platform for a comprehensive list of registered tests.

Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
Alpha-1 Antitrypsin Deficiency				
SERPINA1 Known Familial Variant Analysis	*SERPINA1* Targeted Variant Analysis (PreventionGenetics, part of Exact Sciences)	81403	E88.01	5
SERPINA1 Common Variant Analysis or Sequencing and/or	Alpha-1 Antitrypsin (AAT) Mutation Analysis (Quest Diagnostics)	81332	E88.01	1
	SERPINA1 Full Gene Sequencing and Deletion/Duplication (Invitae)	81479		

Deletion/Duplication Analysis				
Other Covered Lung Disorders				
Other Covered Lung Disorders	See list below	81400-81408		2, 3, 4

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 and Molecular 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 (81332, 81403) is considered **medically necessary** when:

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

II. *SERPINA1* targeted variant analysis for a known familial variant (81332, 81403) is considered **investigational** for all other indications.

SERPINA1 Common Variant Analysis or Sequencing and/or Deletion/Duplication Analysis

I. *SERPINA1* common variant analysis (81332) or sequencing and/or deletion/duplication 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 120 mg/dL) or borderline (90-140 mg/dL) alpha-1 antitrypsin levels (as measured by nephelometry), **AND**

   B. Any of the following:

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

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

back to top

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 and Molecular 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.

back to top

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

back to top

BACKGROUND AND RATIONALE

ALPHA-1 ANTITRYPSIN DEFICIENCY

SERPINA1 Known Familial Variant Analysis

Genetic Support Foundation

The Genetic Support Foundation's Genetics 101 information on genetic testing says the following about testing for familial pathogenic variants:

Genetic testing for someone who may be at risk for an inherited disease is always easier if we know the specific genetic cause. Oftentimes, the best way to find the genetic cause is to start by testing someone in the family who is known or strongly suspected to have the disease. If their testing is positive, then we can say that we have found the familial pathogenic (harmful) variant. We can use this as a marker to test other members of the family to see who is also at risk.

SERPINA1 **Common Variant Analysis or Sequencing and/or Deletion/Duplication Analysis**

American Thoracic Society and European Respiratory Society

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

A normal range of plasma alpha-1 antitrypsin (measured via nephelometry) is 83/120 - 200/220 mg/dL. Individuals with borderline normal levels of plasma alpha-1 antitrypsin (90-140 mg/dL) or with abnormally low levels (below 120 mg/dL) should be evaluated for alpha-1 antitrypsin deficiency. (p. 826)

“The following features should prompt suspicion by physicians that their patient may be more likely to have AAT deficiency:

- Early-onset emphysema (age of 45 years or less)
- Emphysema in the absence of a recognized risk factor (smoking, occupational dust exposure, etc.)
- Emphysema with prominent basilar hyperlucency
- Otherwise unexplained liver disease
- Necrotizing panniculitis
- Anti-proteinase 3-positive vasculitis (C-ANCA [anti-neutrophil cytoplasmic antibody]-positive vasculitis)
- Family history of any of the following: emphysema, bronchiectasis, liver disease, or panniculitis
- Bronchiectasis without evident etiology…” (p. 820)

The statement also recommended that individuals with a sibling with AAT deficiency should also be offered genetic testing. (p. 827)

back to top

REFERENCES

1. American Thoracic Society; European Respiratory Society. American Thoracic Society/European Respiratory Society statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. Am J Respir Crit Care Med. 2003;168(7):818-900. doi:10.1164/rccm.168.7.818
2. Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1116/
3. Online Mendelian Inheritance in Man, OMIM®. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD). World Wide Web URL: https://omim.org/
4. MedlinePlus [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: https://medlineplus.gov/genetics/.
5. Genetic Support Foundation. Genetics 101 Genetic Testing: Familial Pathogenic Variant. Accessed 10/4/2022. https://geneticsupportfoundation.org/genetics-101/#

back to top