Clinical Policy: Genetic Testing Lung Disorders

Reference Number: CP.MP.228
Date of Last Revision: 02/22

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

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 member/enrollee.

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

CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
81403	SERPINA Targeted Mutation Analysis	SERPINA1 Known Familial Variant Analysis	E88.01
81332	SERPINA1 Common Variant Analysis	SERPINA1 Common Variant Analysis or Sequencing Analysis	E88.01
81479	SERPINA1 Sequencing Analysis	SERPINA1 Common Variant Analysis or Sequencing Analysis	E88.01
81400-81408	See list below	Other Covered Lung Disorders	N/A

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

- ***CP.MP.230 Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay*** for criteria related to diagnostic testing for cystic fibrosis and other multisystem inherited disorders.
- ***CP.MP.222 Genetic Testing: General Approach to Genetic Testing*** for criteria related to genetic testing for lung disorders and disease that are not specifically discussed in this or another non-general policy.

Policy/Criteria

Alpha-1 Antitrypsin Deficiency

SERPINA1 Known Familial Variant Analysis

I. It is the policy of health plans affiliated with Centene Corporation® that *SERPINA1* targeted variant analysis for a known familial variant (81403) is considered **medically necessary** when:

   A. The member/enrollee has a close relative[1a] with a known pathogenic or likely pathogenic variants in *SERPINA1*.

II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support *SERPINA1* targeted variant analysis for a known familial variant (81403) for all other indications.

SERPINA1 Common Variant Analysis or Sequencing Analysis

I. It is the policy of health plans affiliated with Centene Corporation® that *SERPINA1* common variant analysis (81332) or sequencing analysis (81479) to establish a diagnosis of alpha-1 antitrypsin (AAT) deficiency is considered **medically necessary** when meeting both of the following:

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

   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. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support *SERPINA1* common variant analysis (81332) or sequencing analysis (81479) to establish a diagnosis of alpha-1 antitrypsin deficiency for all other indications.

Other Covered Lung Disorders

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

I. It is the policy of health plans affiliated with Centene Corporation® that genetic testing to establish or confirm one of the following genetic lung disorders to guide management is considered **medically necessary** when the member/enrollee 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. It is the policy of health plans affiliated with Centene Corporation® that 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 CP.MP.222 *General Approach to Genetic Testing* (see policy for 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.

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

Background

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 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

European Respiratory Society

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.

Coding Implications

Reviews, Revisions, and Approvals	Revision Date	Approval Date
Policy developed.	02/22	02/22

References

1. Stoller JK, Hupertz V, Aboussouan LS. Alpha-1 Antitrypsin Deficiency. 2006 Oct 27 [Updated 2020 May 21]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1519/
2. Miravitlles M, Dirksen A, Ferrarotti I, et al. European Respiratory Society statement: diagnosis and treatment of pulmonary disease in α1-antitrypsin deficiency. Eur Respir J. 2017;50(5):1700610. Published 2017 Nov 30. doi:10.1183/13993003.00610-2017
3. Alpha 1-antitrypsin deficiency: memorandum from a WHO meeting. Bull World Health Organ. 1997;75(5):397-415.
4. 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
5. Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1116/
6. Online Mendelian Inheritance in Man, OMIM®. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD). World Wide Web URL: https://omim.org/
7. MedlinePlus [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: https://medlineplus.gov/genetics/

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved.

"Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of member/enrollee. This clinical policy is not intended to recommend treatment for member/enrollee. Member/enrollee should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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Note: For Medicaid members/enrollees, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Note: For Medicare members/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at http://www.cms.gov for additional information.