BSC_CON_2.23	Genetic Testing: Lung Disorders		
Original Policy Date:	December 1, 2023	**Effective Date:**	December 1, 2023
Section:	2.0 Medicine	**Page:**	Page 1 of 8

Example Test 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.

Policy Statement Locations	Example Tests, Labs	Common CPT Codes
Alpha-1 Antitrypsin Deficiency		
SERPINA1 Known Familial Variant Analysis	*SERPINA1* Targeted Variant Analysis (PreventionGenetics, part of Exact Sciences)	81403
SERPINA1 Common Variant Analysis or Sequencing and/or Deletion/Duplication Analysis	Alpha-1 Antitrypsin (AAT) Mutation Analysis (Quest Diagnostics)	81332
	SERPINA1 Full Gene Sequencing and Deletion/Duplication (Invitae)	81479
Other Covered Lung Disorders		
Other Covered Lung Disorders	See list below	81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408

Policy Statement

SERPINA1 Known Familial Variant Analysis

I. *SERPINA1* targeted variant analysis for a known familial variant (81332, 81403) may be 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

III. *SERPINA1* common variant analysis (81332) or sequencing and/or deletion/duplication analysis (81479) to establish a diagnosis of alpha-1 antitrypsin (AAT) deficiency may be considered **medically necessary** when the member has **both** of the following:
   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)
   B. **Any** of the following:
      1. Early-onset emphysema (45 years of age or younger)
      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 Alpha-1-antitrypsin (AAT) deficiency

IV. *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.

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.

V. Genetic testing to establish or confirm one of the following genetic lung disorders to guide management may be considered **medically necessary** when the member demonstrates clinical features* consistent with the disorder (the list is not meant to be comprehensive, see IV below):
   A. Familial Pulmonary Fibrosis
   B. Primary Ciliary Dyskinesia
   C. Pulmonary lymphangioleiomyomatosis (LAM)
   D. Pulmonary alveolar proteinosis (PAP)

VI. 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.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

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

Description

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.

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. ***(to be published)***

- ***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.

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

- N/A

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.

Alpha-1 Antitrypsin Deficiency - *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)

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/#

Documentation for Clinical Review

Please provide the following documentation:

- Name of the test being requested or the Concert Genetics GTU identifier. The Concert Genetics GTU can be found at https://app.concertgenetics.com
- CPT codes to be billed for the particular genetic test (GTU required for unlisted codes)
- History and physical and/or consultation notes including:
  - Clinical findings:
    - Signs/symptoms leading to a suspicion of genetic condition
    - Family history if applicable
  - Prior evaluation/treatment:
    - Previous test results (i.e., imagining, lab work, etc.) related to reason for genetic testing
    - Family member's genetic test result, if applicable
  - Rationale
    - Reason for performing test
    - How test result will impact clinical decision making

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	81332	SERPINA1 (serpin peptidase inhibitor, clade A, alpha-1 antiproteinase, antitrypsin, member 1) (e.g., alpha-1-antitrypsin deficiency), gene analysis, common variants (e.g., *S and *Z)
	81400	Molecular Pathology Procedure Level 1
	81401	Molecular Pathology Procedure Level 2
	81402	Molecular Pathology Procedure Level 3
	81403	Molecular Pathology Procedure Level 4
	81404	Molecular Pathology Procedure Level 5
	81405	Molecular Pathology Procedure Level 6
	81406	Molecular Pathology Procedure Level 7
	81407	Molecular Pathology Procedure Level 8
	81408	Molecular Pathology Procedure Level 9
	81479	Unlisted molecular pathology procedure
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
12/01/2023	New policy.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and

effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE	**AFTER**
New Policy **Policy Statement:** N/A	**Genetic Testing: Lung Disorders BSC_CON_2.23** **Policy Statement:** ***SERPINA1* Known Familial Variant Analysis** I. *SERPINA1* targeted variant analysis for a known familial variant (81332, 81403) may be 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** III. *SERPINA1* common variant analysis (81332) or sequencing and/or deletion/duplication analysis (81479) to establish a diagnosis of alpha-1 antitrypsin (AAT) deficiency may be considered **medically necessary** when the member has **both** of the following: 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) B. **Any** of the following: 1. Early-onset emphysema (45 years of age or younger) 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 Alpha-1-antitrypsin (AAT) deficiency IV. *SERPINA1* common variant analysis (81332) or sequencing and/or deletion/duplication analysis (81479) to establish a diagnosis of

POLICY STATEMENT	
BEFORE	**AFTER**
	alpha-1 antitrypsin deficiency is considered **investigational** 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, it may be appropriate to cover these genetic tests to establish or confirm a diagnosis. V. Genetic testing to establish or confirm one of the following genetic lung disorders to guide management may be considered **medically necessary** when the member demonstrates clinical features* consistent with the disorder (the list is not meant to be comprehensive, see IV below): A. Familial Pulmonary Fibrosis B. Primary Ciliary Dyskinesia C. Pulmonary lymphangioleiomyomatosis (LAM) D. Pulmonary alveolar proteinosis (PAP) VI. 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.