Genetic Testing for Alpha1-Antitrypsin Deficiency

Policy # 00664
Original Effective Date: 07/01/2019
Current Effective Date: 05/11/2020

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider genetic testing for alpha1-antitrypsin deficiency to be **eligible for coverage**** when either of the following conditions are met**:**

Patient Selection Criteria

Coverage eligibility will be considered when either of the following conditions are met:

1. Patient is suspected of having alpha$_1$-antitrypsin deficiency because of clinical factors and/or because the patient may be at high risk of having alpha$_1$-antitrypsin deficiency due to a first-degree relative with alpha$_1$-antitrypsin deficiency (see Policy Guidelines section); OR
2. Patient has a serum alpha$_1$-antitrypsin level in the range of severe deficiency (level less than 11μmol, see policy guideline section).

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers genetic testing for alpha1-antitrypsin deficiency in all other situations to be **investigational.***

©2020 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.

Genetic Testing for Alpha1-Antitrypsin Deficiency

Policy # 00664
Original Effective Date: 07/01/2019
Current Effective Date: 05/11/2020

Policy Guidelines

According to the 2003 joint statement on diagnosis and management of alpha$_1$-antitrypsin deficiency by the American Thoracic Society and European Respiratory Society, the following features should prompt suspicion by physicians that their patient may be more likely to have alpha$_1$-antitrypsin deficiency.

Clinical factors:

- Early-onset emphysema (age ≤45 years)
- Emphysema in the absence of a recognized risk factor (eg, smoking, occupational dust exposure)
- Emphysema with prominent basilar hyperlucency
- Otherwise unexplained liver disease
- Necrotizing panniculitis
- Anti-proteinase 3-positive vasculitis (cytoplasmic anti-neutrophil cytoplasmic antibody–positive vasculitis)
- Bronchiectasis without evident etiology.

Family history:

- A first-degree relative is defined as a parent, child, or sibling.

Table PG1 shows the range of serum levels of alpha$_1$-antitrypsin by common phenotypes according to the commercial standard milligram per deciliter and the purified standard micromole. A level less than 11 μmol is generally considered to be associated with an increased risk of clinical disease, but this cutoff may vary by the specific test used (American Thoracic Society & European Respiratory Society, 2003; Global Initiative for Chronic Obstructive Lung Disease, 2016)

Table PG1. Range of Alpha$_1$-Antitrypsin Serum Levels by Common Phenotypes

	MM	MZ	SS	SZ	ZZ	Znull	Null-Null
Mmol	20-48	17-33	15-33	8-16	2.5-7	<2.5	0
mg/dL	150-350	90-210	100-200	75-120	20-45	<20	0

©2020 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.

Genetic Testing for Alpha1-Antitrypsin Deficiency

Policy # 00664
Original Effective Date: 07/01/2019
Current Effective Date: 05/11/2020

Genetics Nomenclature Update
The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG2). The Society's nomenclature is recommended by the Human Variome Project, the HUman Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG3 shows the recommended standard terminology-"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"-to describe variants identified that cause Mendelian disorders.

Table PG2. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG3. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

©2020 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.

Genetic Counseling
Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Background/Overview

Alpha$_1$-antitrypsin deficiency
Alpha$_1$-antitrypsin deficiency (AATD) is an autosomal recessive genetic disorder that decreases the production of functional alpha$_1$-antitrypsin (AAT) protein or results in production of abnormal types of the protein that are functionally deficient. Data from screening studies have found the prevalence of AATD in the United States to be between 1 in 2857 and 1 in 5097 individuals.

AAT is an acute phase glycoprotein, primarily synthesized in the liver and secreted into the bloodstream. One of the primary functions of the AAT protein is to protect the lungs from damage by the enzyme elastase. Elastase, part of the normal response to injury and inflammation, breaks down proteins and can damage lung tissue if its action is not regulated by AAT. Individuals with AATD thus have an increased risk of lung disease.

AATD Genetics
Production of AAT is encoded by the *SERPINA1* gene, which is codominant (each gene copy is responsible for producing half of the AAT). Although there are more than 75 sequence variants of the *SERPINA1* gene (ie, 75 possible alleles), only a few are common in North America. Approximately 95% of individuals have 2 copies of the normal M allele sequence (MM) and have mean serum AAT concentrations ranging from 20 to 53 μmol/L. The most common abnormal forms are the Z and the S alleles. Individuals with 2 copies of the Z allele (ZZ) tend to be most severely affected, with mean serum AAT concentrations of 2.5 to 7 μmol/L and a high risk of chronic obstructive pulmonary disease. Individuals with genotype SS and heterozygous individuals with genotype MZ have a low risk of chronic obstructive pulmonary disease and moderately lower levels

©2020 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.

of AAT. Individuals with rarer pathogenic variants of the *SERPINA1* gene or null alleles may not produce any AAT and are also at high risk.

Clinical Presentation
AATD is a multisystem disease, primarily affecting the lungs and liver, and less commonly the skin. It may present differently at different ages.

Pulmonary Manifestations
Respiratory disease tends to be more severe and occur sooner (ie, between ages 40 and 50 years) in individuals with AATD who smoke cigarettes and/orare exposed to occupational dust or fumes. In nonsmokers and individuals without environmental exposure, the onset of respiratory disease occurs more commonly in the sixth decade. Childhood-onset lung disease is rare with AATD.

Liver Manifestations
Adults with AATD-associated liver disease generally present with cirrhosis and fibrosis. In contrast, newborns with AATD can present with cholestasis or (less frequently) hepatomegaly and elevated aminotransferase levels. The AATD-associated cholestasis is typically associated with PI*Z homozygotes or PI*SZ heterozygotes, which tend to have less severe lung disease in adulthood. AATD-associated-cholestatic jaundice can progress to require a liver transplant in newborns. In a large series (1976) of 127 newborns with AATD found by screening, the prevalence of liver damage was 11%, severe in about two-thirds of cases.

Skin Manifestations
Panniculitis is a rare, but well-recognized complication of AATD. This dermatologic condition is characterized by inflammatory and necrotizing lesions of the skin and subcutaneous tissue.

Clinical Management
The primary interventions to prevent or treat lung-related symptoms in adults with AATD involve behavioral change, especially avoiding or quitting cigarette smoking. Smoking is the most important risk factor for the development of emphysema in AATD in individuals who are homozygous for the most severe AAT pathogenic variants. In addition, individuals with AATD are advised to avoid other substances that can irritate the lungs (eg, cigarette smoke, dust, workplace chemicals), as well as substances that can cause liver damage (eg, alcohol). There are also general recommendations to exercise, avoid stress, and have a nutritious diet. Furthermore, patients with AATD may be

©2020 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.

recommended to have earlier or more aggressive treatments for conditions such as asthma outbreaks or acute exacerbations of chronic obstructive pulmonary disease. One treatment option that is specific to AATD is AAT augmentation. There are commercially available intravenous AAT augmentation products; patients generally receive injections of plasma every 3 to 4 weeks for life. Inhaled AAT augmentation therapy is under development. There is no consensus on the efficacy of augmentation treatment. Product labels state that the effect of augmentation therapy on emphysema progression and pulmonary exacerbations has not been demonstrated in randomized controlled trials.

Other aspects of AATD management involve monitoring for and screening for comorbidities, including liver disease.

Diagnostic Testing for AAT

Several types of tests are available for patients suspected of having AATD. A blood test is available that quantifies the total amount of AAT in the blood, detecting decreases in AAT protein levels, but not distinguishing among abnormal protein types. AAT is an acute phase reactant, and levels will be elevated in acute and chronic inflammatory conditions, infections, and some cancers, which may cause levels to appear normal in individuals with mild-to-moderate AATD. In general, a serum AAT concentration less than 15% to 20% of the normal value is highly suggestive of a homozygous AAT pathogenic variant.

The alpha$_1$phenotype test identifies the type of circulating AAT protein in the blood by isoelectric focusing of the various AAT protein types. Patterns of protein migration in an electric field are evaluated and compared with normal patterns to determine if and what type of abnormal AAT protein may be present.

Genetic testing for AATD can be done with the alpha$_1$genotype test. This test uses polymerase chain reaction analysis or nucleic acid-based analysis to identify abnormal alleles of AAT DNA. Currently, available genotype tests are only designed to detect the most common pathogenic variants (ie, S and Z alleles).

There are several testing approaches to detect AATD. One is to initially perform serum quantitation, and then, if the AAT level is found to be low, a follow-up phenotype or genotype test is ordered. Another approach is to perform serum protein quantification, followed by genotype

©2020 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.

testing in subjects with clinical suspicion of AATD. If these tests are discordant, phenotype testing is then performed.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

In 2007, the phenotyping test Hydragel 18 A1AT ISOFOCUSING kit (Sebia, GA) was cleared for marketing by the U.S. Food and Drug Administration through the 510(k) process for the qualitative detection and identification of the phenotypes of AAT protein. Food and Drug Administration product code: OBZ.

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the Food and Drug Administration has chosen not to require any regulatory review of this test.

Rationale/Source

Alpha$_1$-antitrypsin deficiency (AATD) is an autosomal recessive genetic disorder that results in decreased production of functional alpha1-antitrypsin (AAT) protein or production of abnormal types of the protein that are functionally deficient. Individuals with AATD, especially smokers, have an increased risk of lung and liver disease. Available tests measure serum AAT levels and phenotype AAT protein variants. Genetic testing is also available to detect the most common pathogenic variants associated with AATD.

For individuals who have suspected AATD who receive genetic testing for AATD, the evidence includes studies on clinical validity, and several controlled studies assessing potential clinical utility. Relevant outcomes are test accuracy and validity, symptoms, and morbid events. Genetic testing can confirm a diagnosis of AATD suggested by serum testing by identifying the known genetic variants associated with the disease and identify AATD when a diagnosis is uncertain due to the suspicious clinical presentation that is not confirmed by serum testing. A chain of evidence suggests that making a diagnosis of AATD in individuals with suspected AATD can support clinical utility by allowing monitoring for multisystem complications and initiation of accepted therapies. Knowledge of AATD status may lead to behavior changes or changes in medical management that lead to improved health

©2020 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.

outcomes; however, there is limited supportive evidence. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

As reflected by clinical guidelines, it is generally accepted that knowledge of AATD status could lead to behavioral change and change in treatment that can lead to an improvement in health outcomes and that genetic testing to confirm a diagnosis of AATD is a reasonable clinical practice. Thus, genetic testing of individuals with suspected AATD and serum AAT level in the range of severe deficiency may be considered medically necessary.

Supplemental Information

Practice Guidelines and Position Statements

Canadian Thoracic Society

In 2012, the Canadian Thoracic Society published clinical practice guidelines on alpha$_1$-antitrypsin deficiency (AATD) testing and alpha$_1$-antitrypsin (AAT) augmentation therapy. The recommendations for targeted testing for AATD included:

- Targeted testing for AATD may be considered in those individuals with chronic obstructive pulmonary disease (COPD) who were either diagnosed before 65 years of age or who had less than a 20 pack-year history of smoking.
- Targeted testing for AATD was not recommended in individuals with bronchiectasis or asthma.

American Thoracic Society and European Respiratory Society

In 2003, the American Thoracic Society and European Respiratory Society published joint recommendations on the diagnosis and management of individuals with AATD. Table 1 summarizes the relevant recommendations.

Table 1. Recommendations for Diagnosis and Management of AATD

Recommendations for Diagnostic Testing	GOR[a]
• "Symptomatic adults with emphysema, chronic obstructive pulmonary disease (COPD), or asthma with airflow obstruction that is not completely reversible with aggressive treatment with bronchodilators….	A

©2020 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.

Recommendations for Diagnostic Testing	GOR[a]
• "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"	
• "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"	B
• "Adults with asthma in whom airflow obstruction is completely reversible	C

©2020 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.

Recommendations for Diagnostic Testing	GOR[a]
• "Predispositionaltesting" • "Population screening of smokers with normal spirometry"	
• "Predispositional fetal testing" • "Population screening of either neonates, adolescents, or adults"[b]	D

AAT: alpha$_1$-antitrypsin; AATD: alpha$_1$-antitrypsin deficiency; C-ANCA: cytoplasmic anti-neutrophil cytoplasmic antibodies; COPD: chronic obstructive pulmonary disease; GOR grade of recommendation.

[a] Type A: genetic testing is recommended; type B: genetic testing should be discussed and could be accepted or declined; type C: genetic testing is not recommended (ie, should not be encouraged); type D: recommend against genetic testing (ie, should be discouraged).

[b] Population screening is not recommended currently. However, a possible exception (type B recommendation) may apply in countries satisfying all three of the following conditions: (1) the prevalence of AAT deficiency is high (about 1/1500, or more); (2) smoking is prevalent; and (3) adequate counseling services are available.

European Respiratory Society

In 2017, the European Respiratory Society published an updated statement on the diagnosis and treatment of pulmonary disease with AATD. Statements relating to genetic testing include:

- Quantitative determination of AAT levels is the crucial first step in identifying AATD, which 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, including the rare 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 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 counseling.

©2020 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.

World Health Organization
A 1997 memorandum. published by the World Health Organization following a 1996 meeting on AATD, included the following recommendations relevant to this review:

- "All patients with COPD and adults and adolescents with asthma [should] be screened once for AAT deficiency using a quantitative test. Those with abnormal results on screening should undergo PI [protease inhibitor] typing.
- "Neonatal AAT screening programs should be undertaken in all developed countries with Caucasian populations." Among research needs listed is an "Analysis of the costs and benefits of screening, as a prelude to implementing neonatal screening for AAT deficiency."
- "There is an urgent need for randomized clinical trials of the efficacy of AAT augmentation therapy in persons with the deficiency."

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01983241[a]	Efficacy and Safety of Alpha1-Proteinase Inhibitor (Human), Modified Process (Alpha-1 MP) in Subjects With Pulmonary Emphysema Due to Alpha1 Antitrypsin Deficiency (AATD) (SPARTA)	339	Aug 2023
NCT00500123	Alpha-1 Coded Testing(ACT) Study	50,000	Jan 2050

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

©2020 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.

References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, "Genetic Testing for Alpha1-Antitrypsin Deficiency", 2.04.79, February 2020.
2. 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. Oct 01 2003;168(7):818-900. PMID 14522813
3. Kelly E, Greene CM, Carroll TP, et al. Alpha-1 antitrypsin deficiency. Respir Med. Jun 2010;104(6):763-772. PMID 20303723
4. Sveger T. Liver disease in alpha1-antitrypsin deficiency detected by screening of 200,000 infants. N Engl J Med. Jun 10 1976;294(24):1316-1321. PMID 1083485
5. Stoller JK, Lacbawan FL, Aboussouan LS. Alpha-1 antitrypsin deficiency. In: Adam M, Ardinger H, Pagon R, et al., eds. GeneReviews. Seattle, WA: University of Washington; 2017.
6. CSL Behring LLC. Zemaira, Alpha1-Proteinase Inhibitor (Human): Package Insert. 2015 Sep; http://labeling.cslbehring.com/PI/US/Zemaira/EN/Zemaira-Prescribing-Information.pdf.
7. Baxter Healthcare Corp. GLASSIA (Alpha1-Proteinase Inhibitor (Human)): Package Insert. 2010 Aug; https://www.fda.gov/media/78773/download
8. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for Diagnosis, Management, and Prevention of COPD 2016. 2016; http://goldcopd.org/global-strategy-diagnosis-management-prevention-copd- 2016/.
9. Food and Drug Administration (FDA). 510(k) substantial equivalence determination decision summary (K063498). n.d.; http://www.accessdata.fda.gov/cdrh_docs/reviews/K063498.pdf.
10. Greulich T, Averyanov A, Borsa L, et al. European screening for alpha1 -antitrypsin deficiency in subjects with lung disease. Clin Respir J. Jan 2017;11(1):90-97. PMID 25919395
11. Sorroche PB, Fernandez Acquier M, Lopez Jove O, et al. Alpha-1 antitrypsin deficiency in COPD patients: a cross-sectional study. Arch Bronconeumol. Nov 2015;51(11):539-543. PMID 25800328
12. Ljujic M, Topic A, Divac A, et al. Isoelectric focusing phenotyping and denaturing gradient gel electrophoresis genotyping: a comparison of two methods in detection of alpha-1-antitrypsin variants. Transl Res. May 2008;151(5):255-259. PMID 18433707
13. Beletic A, Dudvarski-Ilic A, Milenkovic B, et al. Is an integrative laboratory algorithm more effective in detecting alpha-1-antitrypsin deficiency in patients with premature chronic obstructive pulmonary disease than AAT concentration based screening approach? Biochem Med (Zagreb). Jun 2014;24(2):293-298. PMID 24969923

©2020 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.

14. Lerman C, Gold K, Audrain J, et al. Incorporating biomarkers of exposure and genetic susceptibility into smoking cessation treatment: effects on smoking-related cognitions, emotions, and behavior change. Health Psychol. Jan 1997;16(1):87-99. PMID 9028818
15. Audrain J, Boyd NR, Roth J, et al. Genetic susceptibility testing in smoking-cessation treatment: one-year outcomes of a randomized trial. Addict Behav. Nov-Dec 1997;22(6):741-751. PMID 9426791
16. Carpenter MJ, Strange C, Jones Y, et al. Does genetic testing result in behavioral health change? Changes in smoking behavior following testing for alpha-1 antitrypsin deficiency. Ann Behav Med. Feb 2007;33(1):22-28. PMID 17291167
17. Gotzsche PC, Johansen HK. Intravenous alpha-1 antitrypsin augmentation therapy for treating patients with alpha-1 antitrypsin deficiency and lung disease. Cochrane Database Syst Rev. Sep 20 2016;9:CD007851. PMID 27644166
18. Dirksen A, Dijkman JH, Madsen F, et al. A randomized clinical trial of alpha(1)-antitrypsin augmentation therapy. Am J Respir Crit Care Med. Nov 1999;160(5 Pt 1):1468-1472. PMID 10556107
19. Dirksen A, Piitulainen E, Parr DG, et al. Exploring the role of CT densitometry: a randomised study of augmentation therapy in alpha1-antitrypsin deficiency. Eur Respir J. Jun 2009;33(6):1345-1353. PMID 19196813
20. Chapman KR, Burdon JG, Piitulainen E, et al. Intravenous augmentation treatment and lung density in severe alpha1 antitrypsin deficiency (RAPID): a randomised, double-blind, placebo-controlled trial. Lancet. Jul 25 2015;386(9991):360-368. PMID 26026936
21. Marciniuk DD, Hernandez P, Balter M, et al. Alpha-1 antitrypsin deficiency targeted testing and augmentation therapy: a Canadian Thoracic Society clinical practice guideline. Can Respir J. Mar-Apr 2012;19(2):109-116. PMID 22536580
22. Miravitlles M, Dirksen A, Ferrarotti I, et al. European Respiratory Society statement: diagnosis and treatment of pulmonary disease in 1-antitrypsin deficiency. European Respiratory Journal. 2017 Nov 1;50(5):1700610. PMID 29191952.
23. Alpha 1-antitrypsin deficiency: memorandum from a WHO meeting. Bull World Health Organ. Jan 1997;75(5):397-415. PMID 9447774

Policy History

Original Effective Date: 07/01/2019
Current Effective Date: 05/11/2020
04/04/2019 Medical Policy Committee review

©2020 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.

Genetic Testing for Alpha1-Antitrypsin Deficiency

Policy # 00664
Original Effective Date: 07/01/2019
Current Effective Date: 05/11/2020

04/24/2019 Medical Policy Implementation Committee approval. New policy.
04/02/2020 Medical Policy Committee review
04/08/2020 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
Next Scheduled Review Date: 04/2021

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2019 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	81332
HCPCS	G0452

©2020 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.

Genetic Testing for Alpha1-Antitrypsin Deficiency

Policy # 00664
Original Effective Date: 07/01/2019
Current Effective Date: 05/11/2020

ICD-10 Diagnosis	E88.01

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and 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 that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally

©2020 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.

recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

©2020 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.