

## Corporate Medical Policy

### Testing for Alpha-1 Antitrypsin Deficiency AHS-M2068

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#### Description of Procedure or Service

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##### Description

Alpha 1-antitrypsin deficiency (AATD) is a genetic disease that causes deficient or defective production of the alpha-1 antitrypsin (AAT) protease inhibitor that can affect the lungs, liver, and skin (J. Stoller, 2018b).

**\*\*\*Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

#### Policy

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**BCBSNC will provide coverage for testing for alpha-1 antitrypsin deficiency when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.**

#### Benefits Application

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This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

#### When Testing for Alpha-1 Antitrypsin Deficiency is covered

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##### *Serum Testing*

1. Serum quantification of alpha-1 antitrypsin protein and/or A1AT phenotyping by isoelectric focusing or A1AT proteotyping (Pi-typing or protease inhibitor typing) for Z and S alleles by liquid chromatography-tandem mass spectrometry is considered medically necessary in the following situations:
  - a. Symptomatic adults with emphysema, COPD or asthma
  - b. Individuals with unexplained liver disease
  - c. Individuals with persistent obstruction on pulmonary function tests without identifiable risk factors (e.g. cigarette smoking, occupational exposure)
  - d. Adults with necrotizing panniculitis
  - e. Siblings of an individual with known alpha-1 antitrypsin (AAT) deficiency
  - f. Individuals with anti-proteinase three-positive vasculitis (C-ANCA [anti-neutrophil cytoplasmic antibody]-positive vasculitis)
  - g. Individuals with bronchiectasis without evident etiology
2. Isoelectric focusing/phenotyping is considered medically necessary when there is strong suspicion of the disease based on laboratory testing and symptoms and individual has a negative

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genotype testing for common variants or discordant results between A1AT serum levels and proteotype.

## *Genetic testing*

3. Genetic testing for alpha-1 antitrypsin deficiency is considered medically necessary in the following situations:
  - a. Patient is suspected of having alpha-1 antitrypsin deficiency because of the following clinical factors
    - i. Early-onset emphysema (age of 45 years or less); OR
    - ii. Emphysema in the absence of a recognized risk factor (smoking, occupational dust exposure, etc.); OR
    - iii. Emphysema with prominent basilar hyperlucency; OR
    - iv. Otherwise unexplained liver disease; OR
    - v. Necrotizing panniculitis; OR
    - vi. Anti-proteinase three-positive vasculitis (C-ANCA [anti-neutrophil cytoplasmic antibody]-positive vasculitis); OR
    - vii. Bronchiectasis without evident etiology; OR
  - b. Patient has discordant results between serum levels and proteotype testing for Z and S alleles by mass spectrometry
4. Genetic testing for alpha-1 antitrypsin deficiency is considered medically necessary for individuals considered high risk of having alpha-1 antitrypsin deficiency due to a first-degree relative with AAT deficiency. Note: first degree relative is defined as a parent, child, or sibling.
5. Full *SERPINA1* gene sequencing is considered medically necessary when there is strong suspicion of the disease based on laboratory testing and symptoms and individual has a negative genotype testing for common variants or discordant results between A1AT serum levels and proteotype or phenotype.

## **When Testing for Alpha-1 Antitrypsin Deficiency is not covered**

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Testing for alpha-1 antitrypsin deficiency is considered investigational in all other situations.

## **Policy Guidelines**

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### **Background**

Alpha-1 antitrypsin (AAT) deficiency is an underrecognized genetic condition that affects approximately 1 in 2,000 to 1 in 5,000 individuals and predisposes to liver disease and early-onset emphysema (J. K. Stoller & Aboussouan, 2012). It is estimated (Campos, Wanner, Zhang, & Sandhaus, 2005) that up to 80,000 to 100,000 people in the United States have the severe form of the disease (homozygous in null or abnormal alleles). There is much variation in the disease prevalence in other nations (de Serres, Blanco, & Fernandez-Bustillo, 2007), but most current estimates are that 3 million people worldwide have severe AATD (J. Stoller, 2020).

Alpha-1 Antitrypsin deficiency (AATD) is a result of abnormal alpha-1 antitrypsin (AAT) protein inherited in an autosomal recessive pattern with codominant expression in which both genes inherited can be active and contribute to the genetic trait they control. AAT is a member of the serine protease inhibitor (Pi) family, referred to as “serpins”, and it inhibits the proteolytic enzymes elastase, trypsin, chymotrypsin, and thrombin. AAT is encoded by the gene *SERPINA1* (J. Stoller, 2018a, 2020).

Due to the numerous alleles associated with AAT, each allele has been given a letter code based on the “electrophoretic mobility of the protein produced”. The normal allele is the “M” allele, and the most common mutation is the “Z” allele. This system applies for each individual allele; for example, a

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homozygous Z genotype would be denoted as “ZZ”. Similarly, a wildtype (or “normal”) genotype would be “MM”. Besides the normal phenotype, the three other categories of AAT include “deficient” in which insufficient AAT is produced; “null” in which no AAT is produced at all; and “dysfunctional” in which a typical amount of AAT is produced, but the AAT protein does not function correctly (J. Stoller, 2018a, 2020).

Initial testing often begins with serum quantification of AAT protein. This can be done through several methods, including immune turbidimetry and nephelometry (J. Stoller, 2018a, 2020). A low level is generally represented by a serum level below 11 micromol/L (less than 57 mg/dl using nephelometry). Due to the variation of reference ranges in different testing methodologies, most labs will complete isoelectric phenotyping on any individual with a serum AAT levels of < 100 mg/dL (18.4 micromol/L). In fact, the American Thoracic Society suggests persons with borderline serum levels (defined as 12-35 micromoles or 90 to 140 mg/dL) have qualitative testing (ATS/ERS, 2003).

Isoelectric immunophenotype testing uses the difference in migration rates of allele variants under isoelectric focusing. For example, the M variant will migrate to the middle of the gel, Z will migrate the slowest, and F migrates quickly to the side closest to the anode. This is not a genetic test. On occasion the results can be inconclusive or discordant with quantitative testing, requiring genotype testing of the most-common variants (J. Stoller, 2020).

Genotype testing for the most common allele variants can be utilized where isoelectric immunophenotype testing is inconclusive. Usually polymerase chain reaction (PCR) or restriction fragment length polymorphism (RFLP) techniques are utilized to determine if the most common alleles are present. When dealing with the possibility of a rare variant or null allele, full gene sequencing can be utilized as a final diagnostic measure (J. Stoller, 2018a, 2020).

The AAT protein is produced in the liver and has a role in protecting lungs from injury by neutrophil elastase, which is secreted by white blood cells as a response to inflammation or infection. If the enzyme remains unchecked by AAT protein, damage to alveoli resulting in chronic obstructive pulmonary disease can occur. This includes emphysema, asthma, bronchiectasis, and spontaneous pneumothorax. Smoking and other environmental exposure can cause further damage (J. Stoller, 2018a, 2018b, 2020).

Abnormal molecules of AAT protein caused by this illness can also cause liver dysfunction. Pathologic polymerization of the variant AAT can occur, resulting in intrahepatocyte accumulation of AAT molecules, leading to cirrhosis, fibrosis, cholestasis, or hepatomegaly. Liver disease is more common in individuals with certain allele combinations. Male gender and obesity may be risk factors for progression to advanced liver disease in adulthood among patients with severe AAT deficiency. In contrast, alcohol use and viral hepatitis do not appear to increase the risk of progressive hepatic failure (J. Stoller, 2018b). AATD is a common genetic cause of liver disease in children (de Serres, Blanco, & Fernandez-Bustillo, 2003).

Skin manifestations of AATD are also recognized. The most commonly associated skin condition is necrotizing panniculitis. In this condition inflammatory skin lesions are thought to be a consequence of the AAT protein loss of function and subsequent unchecked proteolysis enzyme activity in the skin and subcutaneous tissue. Associations between alpha-1 antitrypsin (AAT) and vascular disease, inflammatory bowel disease, glomerulonephritis, and vasculitis have been proposed but not definitively established (J. Stoller, 2018b).

## Validity and Utility

The literature on the analytic and clinical validity of genetic testing for AATD is limited. In addition, few randomized controlled trials (RCTs) have evaluated the impact of AATD testing on patient outcomes. Current evidence-based guidelines (Vogelmeier et al., 2017) for diagnosis and management of AATD recommend specific interventions for patients with emphysema and AATD. AAT augmentation therapy is often prescribed for patients with AATD and chronic obstructive pulmonary

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disorder (COPD). In addition, several studies have documented that the disease is under-recognized with delay in diagnosis of between 5 to 8 years (Barrecheguren et al., 2016; J. K. Stoller et al., 2005).

Snyder et al evaluated the laboratory methods of assessing AATD. Samples from 512 individuals were analyzed, and “A1AT concentrations were measured by nephelometry. Phenotype analysis was performed by isoelectric focusing electrophoresis. The genotype assay detected the S and Z deficiency alleles by a melting curve analysis.” Of these 512 samples, 10 (2%) were discordant between genotype and phenotype. Of these 10 results, 7 were attributed to phenotyping errors. 4% of the samples submitted to genotype and quantitative analysis were “reflexed” to phenotyping, where phenotyping confirmed the genotype result 85% of the time. The investigators concluded, “The combination of genotyping and quantification, with a reflex to phenotyping, is the optimal strategy for the laboratory evaluation of A1AT deficiency (Snyder et al., 2006).”

Sorroche et al examined a cohort of COPD patients and the prevalence of severe AATD. 1002 patients were evaluated, and 785 (78.34%) had normal AAT levels. The remaining 217 patients had low AAT levels, but only 15 patients had a genotype associated with severe AATD. Of these 15 patients, 12 were ZZ and 3 were SZ. Of the 202 other patients, 29 were a Z heterozygote, 25 were an S heterozygote, and 4 were an SS homozygote. 144 patients could not be definitively diagnosed (Sorroche et al., 2015).

Corda et al examined the prevalence of AATD in a supposed “high-risk” area. 817 residents participated, and 67 had low AAT serum levels. 118 residents carried AATD-related alleles, 114 of which were heterozygotes “(46 Z, 52 S, 9 P(brescia), 4 M(wurzburg), 2 I, 1 P(lowell)”. The authors concluded, “the large number of mostly asymptomatic individuals with AATD identified suggests that in high-risk areas adult population screening programs employing the latest genetic methods are feasible (Corda et al., 2011).”

Soriano and colleagues evaluated the prevalence of AATD testing in COPD patients. The patient sample came from “550 UK Optimum Patient Care Research Database general practices”. Out of 107,024 COPD patients, only 2.2% had any record of being tested for AATD. Of those tested, 23.7% were diagnosed with AATD. The investigators also noted that between 1994 and 2013, the incidence of AATD diagnosis increased. The authors concluded “that AATD remains markedly underdiagnosed in COPD patients (Soriano et al., 2018).”

Greulich et al evaluated the results of a large targeted screening program for AATD. The samples were distributed by a German AAT laboratory over a period of 12 years, and 18,638 testing kits were obtained. Of this sample, 6919 carried at least one mutation, and 1835 patients were considered to have severe AATD. 194 of these patients had “rare” genotypes. The authors concluded that “among clinical characteristics, a history of COPD, emphysema, and bronchiectasis were significant predictors for Pi\*ZZ, whereas a history of asthma, cough and phlegm were predictors of not carrying the genotype Pi\*ZZ (Greulich et al., 2016).”

Hamesch et al evaluated the clinical landscape of liver symptoms in patients with AATD, specifically the Pi\*ZZ genotype. 554 patients (403 exploratory cohort, 151 confirmatory cohort) were included and were compared to 234 controls without pre-existing liver disease. The authors found significantly higher levels of serum liver enzymes in the Pi\*ZZ carriers compared to controls, further noting that “significant” fibrosis was suspected in 20%-36% of Pi\*ZZ carriers. Signs of advanced fibrosis were 9 to 20 times more common in carriers compared to non-carriers. Controlled attenuation parameter of  $\geq 280$  dB/m, which suggests “severe” steatosis was detected in 39% of carriers compared to 31% of controls. Finally, Pi\*ZZ carriers were found to have lower serum concentrations of triglyceride, low, and very-low density lipoprotein cholesterol compared to controls, which the authors suggested to represent impaired hepatic secretion of lipid. Overall, the authors concluded that they identified evidence of liver steatosis, impaired liver secretion, liver fibrosis, and that their data could assist in hepatologic management of Pi\*ZZ carriers (Hamesch et al., 2019).

Strnad et al investigated the impact of the Pi\*Z and Pi\*S genotypes on subjects with non-alcoholic fatty liver disease (NAFLD) or alcohol misuse. Separate cohorts of 1184 with NAFLD and 2462 with chronic

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alcohol abuse were included. The authors found Pi\*Z genotypes in 13.8% of patients with cirrhotic NAFLD but only 2.4% of patients without liver fibrosis. From there, the increased risk of NAFLD subjects to develop cirrhosis was found to be 7.3 times higher in Pi\*Z carriers. The Pi\*Z variant was also found in 6.2% of alcohol abusers but only 2.2% of alcohol abusers without significant liver injury. The increased risk was found to be 5.2 times higher in Pi\*Z carriers. The Pi\*S variant was not associated with NAFLD-related cirrhosis and only mildly with alcohol-related cirrhosis (increased risk = 1.47 times). The authors concluded that the Pi\*Z variant was the strongest “single nucleotide polymorphism-based risk factor for cirrhosis in NAFLD and alcohol misuse, whereas the Pi\*S variant confers only a weak risk in alcohol misusers” and remarked that this finding should be considered in future genetic counseling of affected individuals (Strnad et al., 2019).

## Guidelines and Recommendations

### American Thoracic Society/European Respiratory Society (ATS/ERS, 2003)

The ATS/ERS released joint guidelines on the “Diagnosis and Management of Individuals with Alpha-1 Antitrypsin Deficiency.” These recommendations are as follows (ATS/ERS, 2003):

#### Policy Guidelines

Recommendations were classified as follows:

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, i.e., should not be encouraged

Type D: Recommend against genetic testing, i.e., should be discouraged

Type A recommendations for diagnostic testing in the following situations:

1. Symptomatic adults with emphysema, COPD or asthma with airflow obstruction that is not completely reversible with aggressive treatment with bronchodilators
2. Individuals with unexplained liver disease
3. Asymptomatic individuals with persistent obstruction on pulmonary function tests with identifiable risk factors (e.g. cigarette smoking, occupational exposure)
4. Adults with necrotizing panniculitis
5. Siblings of an individual with known alpha-1 antitrypsin (AAT) deficiency

Type B recommendations for diagnostic testing in the following situations:

1. Adults with bronchiectasis without evidence etiology
2. Adolescents with persistent airflow obstruction
3. Asymptomatic individuals with persistent airflow obstruction and no risk factors
4. Adults with C-ANCA positive (anti-proteinase 3-positive) vasculitis
5. Individuals with a family history of COPD or liver disease not known to be attributed to AAT deficiency
6. Distant relatives of an individual who is homozygous for AAT deficiency
7. Offspring or parents of an individual with homozygous AAT deficiency
8. Siblings, offspring, parents or distant relatives of an individual who is heterozygous for AAT deficiency
9. Individuals at high risk of having AAT deficiency-related diseases
10. 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 for diagnostic testing in the following situations:

1. Adults with asthma in whom airflow obstruction is completely reversible
2. Predispositional testing

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## 3. Population screening of smokers with normal spirometry

Type D recommendations for diagnostic testing in the following situations:

1. Predispositional fetal testing
2. Population screening of either neonates, adolescents or adults\*

\* 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 1/1,500, or more); (2) smoking is prevalent; and (3) adequate counseling services are available.

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

### **Clinical Factors**

- 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 three-positive vasculitis (C-ANCA [anti-neutrophil cytoplasmic antibody]-positive vasculitis)
- Bronchiectasis without evident etiology

The ATS/ERS also made statements on serum testing for AATD. "Serum phenotyping by isoelectric focusing performed by a reliable laboratory is the accepted "gold standard" for diagnosing AAT deficiency". The guidelines recommend "that all subjects with COPD or asthma characterized by incompletely reversible airflow obstruction should be tested once for quantitative AAT determination. Also, individuals with evidence of cirrhosis of the liver with no known etiology should be tested for candidate phenotypes (e.g., PI\*ZZ, PI\*MZ, PI\*Mmalton) and testing should be considered in individuals with the syndrome of Wegener's granulomatosis (antiproteinase-3 vasculitis) (ATS/ERS, 2003)."

### **American College of Gastroenterology (ACG) (Kwo, Cohen, & Lim, 2017)**

The ACG recommends the following for AATD:

- "Patients with persistently elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) should undergo screening for alpha-1 antitrypsin (A1AT) deficiency with alpha-1 antitrypsin phenotype."
- "Evaluation of hepatocellular injury (defined by the guidelines as "disproportionate elevation of AST and ALT levels compared with alkaline phosphatase levels") includes testing for A1AT deficiency (Kwo, Cohen, & Lim, 2017)"

### **World Health Organization (WHO, 1997)**

The WHO released a memorandum on AATD regarding AATD's association with conditions such as COPD and asthma. Their recommendation is as follows: "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" (WHO, 1997).

### **European Respiratory Society (ERS) (Miravittles et al., 2017)**

The ERS (Miravittles et al., 2017) published updated guidelines which recommend:

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- “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.”

The ERS has also noted that “there is no evidence to support efficacy of AAT augmentation therapy in PiSZ, PiMZ or current smokers of any protein phenotype (Miravittles et al., 2017).”

## **Alpha-1 Foundation (2016) (Sandhaus et al., 2016)**

The Alpha-1 Foundation (Sandhaus et al., 2016) sponsored a committee of experts to examine all relevant, recent literature in order to provide concise recommendations for the diagnosis and management of individuals with AATD.

- “For family testing after a proband is identified, AAT level testing alone is not recommended because it does not fully characterize disease risk from AATD.”
- “For diagnostic testing of symptomatic individuals, they recommend genotyping for at least the S and Z alleles. Advanced or confirmatory testing should include Pi-typing, AAT level testing, and/or expanded genotyping.”
- “All patients with COPD, unexplained chronic liver disease, necrotizing panniculitis, granulomatosis with polyangiitis, or unexplained bronchiectasis should be tested for AATD.”
- “Parents, siblings, and children, as well as extended family of individuals identified with an abnormal gene for AAT, should be provided genetic counseling and offered testing for AATD (see guideline document for special considerations about testing minors).”

The Foundation also noted the following (these statements were not labeled recommendations):

- “For primary diagnosis of AATD the most sensitive and specific method of diagnosis is direct identification of the Z allele by genotyping. By also including the S allele, genotyping for the S and Z allele is greater than 99% specific and sensitive. “
- “AAT levels are insufficient to identify at risk individuals because the AAT level changes with inflammation, pregnancy, and in children. “
- “The range of serum AAT levels among individuals with specific genotypes is sufficiently broad that there is overlap between different genotypes. Thus, serum AAT levels cannot discriminate between different genotypes and additional AAT testing is needed”

## **Global Initiative for Chronic Obstructive Lung Disease (GOLD, 2020)**

GOLD notes that genes such as MMP-12 may contribute to a decline in lung function. However, they acknowledge that “it remains uncertain whether these are genes are directly responsible for COPD or are merely markers of causal genes (GOLD, 2020).”

## **Canadian Thoracic Society (CTS, 2012) (Marciniuk et al., 2012)**

The CTS released guidelines on genetic testing for AATD, which are as follows:

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- “We suggest targeted testing for A1AT deficiency be considered in individuals with COPD diagnosed before 65 years of age or with a smoking history of <20 pack years. (Grade of recommendation: 2C)”
- “We suggest targeted testing for A1AT deficiency not be undertaken in individuals with bronchiectasis or asthma. (Grade of recommendation: 2C) (Marciniuk et al., 2012)”

## National Institute Health and Care Excellence (NICE, 2019)

NICE published a guideline discussing chronic obstructive pulmonary disease (COPD) in 2019. In it, they note that measurement of serum alpha-1 antitrypsin has a role in identifying deficiencies if the condition is “early onset, [of] minimal smoking history, or [has] family history”.

## Applicable Federal Regulations

A search on the FDA website for the word “antitrypsin” on April 7, 2020, yielded 17 results (FDA, 2020).

On November 17, 2017 the FDA approved Grifols’ (Grifols, 2017) *SERPINA1* Variant Detection System as a qualitative in vitro molecular diagnostic system used to detect variants in *SERPINA1* gene in genomic DNA isolated from human specimens.

On April 6, 2017 the FDA approved (FDA, 2017) the 23andMe PGS Genetic Health Risk Report for Alpha-1 Antitrypsin Deficiency (AATD) which determines if a person has variants associated with a higher risk of developing AATD-associated lung or liver disease. This report is based on a qualitative genetic test for single nucleotide polymorphism detection of the PI\*Z (rs28929474) and PI\*S (rs17580) variants in the *SERPINA1* gene by using the 23andMe Personal Genome Service.

Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA ’88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

## Billing/Coding/Physician Documentation Information

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This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at [www.bcbsnc.com](http://www.bcbsnc.com). They are listed in the Category Search on the Medical Policy search page.

*Applicable service codes: 82103, 82104, 82542, 81332, 81479, 83789*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

## Scientific Background and Reference Sources

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### For policy titled: Genetic Testing for Alpha-1 Antitrypsin Deficiency

ATS/ERS. (2003). 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*, 168(7), 818-900. doi:10.1164/rccm.168.7.818

Barrecheguren, M., Monteagudo, M., Simonet, P., Llor, C., Rodriguez, E., Ferrer, J., . . . Miravittles, M. (2016). Diagnosis of alpha-1 antitrypsin deficiency: a population-based study. *Int J Chron Obstruct Pulmon Dis*, 11, 999-1004. doi:10.2147/copd.s108505



# Testing for Alpha-1 Antitrypsin Deficiency AHS-M2068

- Bowlus, C. L., Willner, I., Zern, M. A., Reuben, A., Chen, P., Holladay, B., . . . Strange, C. (2005). Factors associated with advanced liver disease in adults with alpha1-antitrypsin deficiency. *Clin Gastroenterol Hepatol*, 3(4), 390-396.
- Campos, M. A., Wanner, A., Zhang, G., & Sandhaus, R. A. (2005). Trends in the diagnosis of symptomatic patients with alpha1-antitrypsin deficiency between 1968 and 2003. *Chest*, 128(3), 1179-1186. doi:10.1378/chest.128.3.1179
- de Serres, F. J., Blanco, I., & Fernandez-Bustillo, E. (2007). PI S and PI Z alpha-1 antitrypsin deficiency worldwide. A review of existing genetic epidemiological data. *Monaldi Arch Chest Dis*, 67(4), 184-208. doi:10.4081/monaldi.2007.476
- FDA. (2017). *Decision Summary for 23andMe PGS Genetic Health Risk Report*. U.S. Food and Drug Administration Retrieved from [https://www.accessdata.fda.gov/cdrh\\_docs/reviews/DEN160026.pdf](https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN160026.pdf).
- FDA. (2018a). *Devices@FDA*. U.S. Food and Drug Administration Retrieved from [https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm?start\\_search=1&q=YWxwaGEgMSBhbnRpdHJ5cHNpbG==&approval\\_date\\_from=&approval\\_date\\_to=&sort=approvaldate\\_desc&pagenum=10](https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm?start_search=1&q=YWxwaGEgMSBhbnRpdHJ5cHNpbG==&approval_date_from=&approval_date_to=&sort=approvaldate_desc&pagenum=10).
- FDA. (2018b). *Product Classification*. U.S. Food and Drug Administration Retrieved from <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpdc/classification.cfm?id=pzh>.
- Grifols. (2017). DA approval of genetic test for alpha-1 deficiency and EMA approval of fibrin sealant. Retrieved from <http://www.grifols.com/en/web/international/view-news/-/new/fda-approval-of-genetic-test-for-alpha-1-deficiency-and-ema-approval-of-fibrin-sealant>
- Gross, B., Grebe, M., Wencker, M., Stoller, J. K., Bjursten, L. M., & Janciauskiene, S. (2009). New Findings in PiZZ alpha1-antitrypsin deficiency-related panniculitis. Demonstration of skin polymers and high dosing requirements of intravenous augmentation therapy. *Dermatology*, 218(4), 370-375. doi:10.1159/000202982
- Hartz, P. (2012). Online Mendelian Inheritance in Man (OMIM). from Johns Hopkins University <https://omim.org/entry/107400>
- Kwo, P. Y., Cohen, S. M., & Lim, J. K. (2017). ACG Clinical Guideline: Evaluation of Abnormal Liver Chemistries. *Am J Gastroenterol*, 112(1), 18-35. doi:10.1038/ajg.2016.517 Retrieved from <http://gi.org/wp-content/uploads/2018/04/ACG-Abnormal-Liver-Chemistries-Guideline-Summary.pdf>. doi:10.1038/ajg.2016.517
- Miravittles, M., Dirksen, A., Ferrarotti, I., Koblizek, V., Lange, P., Mahadeva, R., . . . Stockley, R. A. (2017). European Respiratory Society statement: diagnosis and treatment of pulmonary disease in alpha1-antitrypsin deficiency. *Eur Respir J*, 50(5). doi:10.1183/13993003.00610-2017 Retrieved from <http://dx.doi.org/10.1183/13993003.00610-2017>. doi:10.1183/13993003.00610-2017
- Miravittles, M., Herr, C., Ferrarotti, I., Jardi, R., Rodriguez-Frias, F., Luisetti, M., & Bals, R. (2010). Laboratory testing of individuals with severe alpha1-antitrypsin deficiency in three European centres. *Eur Respir J*, 35(5), 960-968. doi:10.1183/09031936.00069709
- Sandhaus, R. A., Turino, G., Brantly, M. L., Campos, M., Cross, C. E., Goodman, K., . . . Teckman, J. (2016). The Diagnosis and Management of Alpha-1 Antitrypsin Deficiency in the Adult. *Chronic Obstr Pulm Dis*, 3(3), 668-682. doi:10.15326/jcopdf.3.3.2015.0182
- Stoller, J. (2018a). Clinical manifestations, diagnosis, and natural history of alpha-1 antitrypsin deficiency - UpToDate. In H. Hollingsworth (Ed.), UpToDate. Retrieved from [https://www.uptodate.com/contents/clinical-manifestations-diagnosis-and-natural-history-of-alpha-1-antitrypsin-deficiency?topicRef=1429&source=see\\_link#H1551012802](https://www.uptodate.com/contents/clinical-manifestations-diagnosis-and-natural-history-of-alpha-1-antitrypsin-deficiency?topicRef=1429&source=see_link#H1551012802).
- Stoller, J. (2018b). Extrapulmonary manifestations of alpha-1 antitrypsin deficiency - UpToDate. In H. Hollingsworth (Ed.), UpToDate. Retrieved from [https://www.uptodate.com/contents/extrapulmonary-manifestations-of-alpha-1-antitrypsin-deficiency?source=see\\_link](https://www.uptodate.com/contents/extrapulmonary-manifestations-of-alpha-1-antitrypsin-deficiency?source=see_link).
- Stoller, J. K., & Aboussouan, L. S. (2012). A review of alpha1-antitrypsin deficiency. *Am J Respir Crit Care Med*, 185(3), 246-259. doi:10.1164/rccm.201108-1428CI
- Stoller, J. K., Sandhaus, R. A., Turino, G., Dickson, R., Rodgers, K., & Strange, C. (2005). Delay in diagnosis of alpha1-antitrypsin deficiency: a continuing problem. *Chest*, 128(4), 1989-1994. doi:10.1378/chest.128.4.1989

# Testing for Alpha-1 Antitrypsin Deficiency AHS-M2068

- Vogelmeier, C. F., Criner, G. J., Martinez, F. J., Anzueto, A., Barnes, P. J., Bourbeau, J., . . . Agusti, A. (2017). Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Lung Disease 2017 Report: GOLD Executive Summary. *Respirology*, 22(3), 575-601. doi:10.1111/resp.13012
- WHO. (1997). Alpha 1-antitrypsin deficiency: memorandum from a WHO meeting. *Bull World Health Organ*, 75(5), 397-415.

## **For policy titled: Testing for Alpha-1 Antitrypsin Deficiency**

- ATS/ERS. (2003). 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*, 168(7), 818-900. doi:10.1164/rccm.168.7.818
- Barrecheguren, M., Monteagudo, M., Simonet, P., Llor, C., Rodriguez, E., Ferrer, J., . . . Miravittles, M. (2016). Diagnosis of alpha-1 antitrypsin deficiency: a population-based study. *Int J Chron Obstruct Pulmon Dis*, 11, 999-1004. doi:10.2147/copd.s108505
- Campos, M. A., Wanner, A., Zhang, G., & Sandhaus, R. A. (2005). Trends in the diagnosis of symptomatic patients with alpha1-antitrypsin deficiency between 1968 and 2003. *Chest*, 128(3), 1179-1186. doi:10.1378/chest.128.3.1179
- Corda, L., Medicina, D., La Piana, G. E., Bertella, E., Moretti, G., Bianchi, L., . . . Balbi, B. (2011). Population genetic screening for alpha1-antitrypsin deficiency in a high-prevalence area. *Respiration*, 82(5), 418-425. doi:10.1159/000325067
- de Serres, F. J., Blanco, I., & Fernandez-Bustillo, E. (2003). Genetic epidemiology of alpha-1 antitrypsin deficiency in North America and Australia/New Zealand: Australia, Canada, New Zealand and the United States of America. *Clin Genet*, 64(5), 382-397.
- de Serres, F. J., Blanco, I., & Fernandez-Bustillo, E. (2007). PI S and PI Z alpha-1 antitrypsin deficiency worldwide. A review of existing genetic epidemiological data. *Monaldi Arch Chest Dis*, 67(4), 184-208. doi:10.4081/monaldi.2007.476
- FDA. (2017). *Decision Summary for 23andMe PGS Genetic Health Risk Report*. U.S. Food and Drug Administration Retrieved from [https://www.accessdata.fda.gov/cdrh\\_docs/reviews/DEN160026.pdf](https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN160026.pdf)
- FDA. (2019). *Devices@FDA*. U.S. Food and Drug Administration Retrieved from [https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm?start\\_search=1&q=YWxwaGEgMSBhbnRpdHJ5cHNpbG==&approval\\_date\\_from=&approval\\_date\\_to=&sort=approvaldate\\_desc&pagenum=10](https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm?start_search=1&q=YWxwaGEgMSBhbnRpdHJ5cHNpbG==&approval_date_from=&approval_date_to=&sort=approvaldate_desc&pagenum=10)
- FDA. (2020). *Devices@FDA*. U.S. Food and Drug Administration Retrieved from <https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm>
- GOLD. (2020). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Retrieved from [https://goldcopd.org/wp-content/uploads/2019/12/GOLD-2020-FINAL-ver1.2-03Dec19\\_WMV.pdf](https://goldcopd.org/wp-content/uploads/2019/12/GOLD-2020-FINAL-ver1.2-03Dec19_WMV.pdf)
- Greulich, T., Nell, C., Herr, C., Vogelmeier, C., Kotke, V., Wiedmann, S., . . . Koczulla, A. R. (2016). Results from a large targeted screening program for alpha-1-antitrypsin deficiency: 2003 - 2015. *Orphanet J Rare Dis*, 11(1), 75. doi:10.1186/s13023-016-0453-8
- Grifols. (2017). DA approval of genetic test for alpha-1 deficiency and EMA approval of fibrin sealant. Retrieved from <http://www.grifols.com/en/web/international/view-news/-/new/fda-approval-of-genetic-test-for-alpha-1-deficiency-and-ema-approval-of-fibrin-sealant>
- Hamesch, K., Mandorfer, M., Pereira, V. M., Moeller, L. S., Pons, M., Dolman, G. E., . . . Strnad, P. (2019). Liver Fibrosis and Metabolic Alterations in Adults With alpha-1-antitrypsin Deficiency Caused by the Pi\*ZZ Mutation. *Gastroenterology*, 157(3), 705-719.e718. doi:10.1053/j.gastro.2019.05.013
- Kwo, P. Y., Cohen, S. M., & Lim, J. K. (2017). ACG Clinical Guideline: Evaluation of Abnormal Liver Chemistries. *Am J Gastroenterol*, 112(1), 18-35. doi:10.1038/ajg.2016.517
- Marciniuk, D. D., Hernandez, P., Balter, M., Bourbeau, J., Chapman, K. R., Ford, G. T., . . . Muthuri, S. (2012). Alpha-1 antitrypsin deficiency targeted testing and augmentation therapy: a Canadian Thoracic Society clinical practice guideline. *Can Respir J*, 19(2), 109-116. doi:10.1155/2012/920918

# Testing for Alpha-1 Antitrypsin Deficiency AHS-M2068

- Miravittles, M., Dirksen, A., Ferrarotti, I., Koblizek, V., Lange, P., Mahadeva, R., . . . Stockley, R. A. (2017). European Respiratory Society statement: diagnosis and treatment of pulmonary disease in alpha1-antitrypsin deficiency. *Eur Respir J*, 50(5). doi:10.1183/13993003.00610-2017
- NICE. (2019). Chronic obstructive pulmonary disease in over 16s: diagnosis and management. Retrieved from <https://www.nice.org.uk/guidance/ng115/chapter/Recommendations>
- Sandhaus, R. A., Turino, G., Brantly, M. L., Campos, M., Cross, C. E., Goodman, K., . . . Teckman, J. (2016). The Diagnosis and Management of Alpha-1 Antitrypsin Deficiency in the Adult. *Chronic Obstr Pulm Dis*, 3(3), 668-682. doi:10.15326/jcopdf.3.3.2015.0182
- Snyder, M. R., Katzmann, J. A., Butz, M. L., Wiley, C., Yang, P., Dawson, D. B., . . . Thibodeau, S. N. (2006). Diagnosis of alpha-1-antitrypsin deficiency: An algorithm of quantification, genotyping, and phenotyping. *Clin Chem*, 52(12), 2236-2242. doi:10.1373/clinchem.2006.072991
- Soriano, J. B., Lucas, S. J., Jones, R., Miravittles, M., Carter, V., Small, I., . . . Mahadeva, R. (2018). Trends of testing for and diagnosis of alpha1-antitrypsin deficiency in the UK: more testing is needed. *Eur Respir J*, 52(1). doi:10.1183/13993003.00360-2018
- Sorroche, P. B., Fernandez Acquier, M., Lopez Jove, O., Giugno, E., Pace, S., Livellara, B., . . . Saez, M. S. (2015). Alpha-1 Antitrypsin Deficiency in COPD Patients: A Cross-Sectional Study. *Arch Bronconeumol*, 51(11), 539-543. doi:10.1016/j.arbres.2015.01.008
- Stoller, J. (2018a). Clinical manifestations, diagnosis, and natural history of alpha-1 antitrypsin deficiency - UpToDate. In H. Hollingsworth (Ed.), *UpToDate*. Retrieved from [https://www.uptodate.com/contents/clinical-manifestations-diagnosis-and-natural-history-of-alpha-1-antitrypsin-deficiency?topicRef=1429&source=see\\_link#H1551012802](https://www.uptodate.com/contents/clinical-manifestations-diagnosis-and-natural-history-of-alpha-1-antitrypsin-deficiency?topicRef=1429&source=see_link#H1551012802)
- Stoller, J. (2018b). Extrapulmonary manifestations of alpha-1 antitrypsin deficiency - UpToDate. In H. Hollingsworth (Ed.), *UpToDate*. Retrieved from [https://www.uptodate.com/contents/extrapulmonary-manifestations-of-alpha-1-antitrypsin-deficiency?source=see\\_link](https://www.uptodate.com/contents/extrapulmonary-manifestations-of-alpha-1-antitrypsin-deficiency?source=see_link)
- Stoller, J. (2020). Clinical manifestations, diagnosis, and natural history of alpha-1 antitrypsin deficiency - UpToDate. In H. Hollingsworth (Ed.), *UpToDate*. Retrieved from [https://www.uptodate.com/contents/clinical-manifestations-diagnosis-and-natural-history-of-alpha-1-antitrypsin-deficiency?topicRef=1429&source=see\\_link#H1551012802](https://www.uptodate.com/contents/clinical-manifestations-diagnosis-and-natural-history-of-alpha-1-antitrypsin-deficiency?topicRef=1429&source=see_link#H1551012802)
- Stoller, J. K., & Aboussouan, L. S. (2012). A review of alpha1-antitrypsin deficiency. *Am J Respir Crit Care Med*, 185(3), 246-259. doi:10.1164/rccm.201108-1428CI
- Stoller, J. K., Sandhaus, R. A., Turino, G., Dickson, R., Rodgers, K., & Strange, C. (2005). Delay in diagnosis of alpha1-antitrypsin deficiency: a continuing problem. *Chest*, 128(4), 1989-1994. doi:10.1378/chest.128.4.1989
- Strnad, P., Buch, S., Hamesch, K., Fischer, J., Rosendahl, J., Schmelz, R., . . . Trautwein, C. (2019). Heterozygous carriage of the alpha1-antitrypsin Pi\*Z variant increases the risk to develop liver cirrhosis. *Gut*, 68(6), 1099-1107. doi:10.1136/gutjnl-2018-316228
- Vogelmeier, C. F., Criner, G. J., Martinez, F. J., Anzueto, A., Barnes, P. J., Bourbeau, J., . . . Agusti, A. (2017). Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Lung Disease 2017 Report: GOLD Executive Summary. *Respirology*, 22(3), 575-601. doi:10.1111/resp.13012
- WHO. (1997). Alpha 1-antitrypsin deficiency: memorandum from a WHO meeting. *Bull World Health Organ*, 75(5), 397-415. Retrieved from [https://apps.who.int/iris/bitstream/handle/10665/55120/bulletin\\_1997\\_75%285%29\\_397-415.pdf?sequence=1&isAllowed=y](https://apps.who.int/iris/bitstream/handle/10665/55120/bulletin_1997_75%285%29_397-415.pdf?sequence=1&isAllowed=y)

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## Policy Implementation/Update Information

### For policy titled: Genetic Testing for Alpha-1 Antitrypsin Deficiency

1/1/2019 BCBSNC will provide coverage for genetic testing for alpha-1 antitrypsin deficiency when it is determined to be medically necessary because the criteria and guidelines are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (jd)

### For policy titled: Testing for Alpha-1 Antitrypsin Deficiency

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- 9/10/2019 Reviewed by Avalon 2<sup>nd</sup> Quarter 2019 CAB with title change. Made the following changes to the When Covered section: reordered and separated indications into two subclasses: serum testing and genetic testing; added indication stating when serum testing of antitrypsin levels is medically necessary; separated IEF and genetic testing indications and made a separate indication for genetic testing of high-risk individuals due to first-degree relative positive for AATD for clarity. Policy guidelines revised and updated. Added the following code to the Billing/Coding section: 81479 and removed code table. References updated. Medical Director review 8/2019. (jd)
- 3/31/20 Specialty Matched Consultant Advisory Panel review 3/2020. Medical Director review 3/2020. (jd)
- 7/28/20 Reviewed by Avalon 2<sup>nd</sup> Quarter 2020 CAB. Policy guidelines and references updated. Medical Director review 7/2020. (jd)

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