PREMERA HMO

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ROUTINE TEST MANAGEMENT POLICY – 15.01.048

Testing for Alpha-1 Antitrypsin Deficiency

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Policy 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 (Stoller, 2024). AAT deficiency results in unbalanced rapid breakdown of proteins, especially in the supporting elastic tissue of the lungs (NORD, 2024a).

Indications

1. For individuals who are suspected of having alpha-1 antitrypsin (AAT) deficiency, serum quantification of alpha-1 antitrypsin (AAT) protein and AAT phenotyping or AAT proteotyping (see Note 1 in **Related Information**) is considered **reimbursable** once per lifetime in any of the following situations:

    a. For symptomatic individuals 18 years or older with emphysema, COPD, or asthma.
    b. For individuals with unexplained liver disease (e.g., chronic hepatitis with or without cirrhosis, chronically elevated aminotransferase levels, portal hypertension, primary liver cancer).
    c. For individuals with persistent obstruction on pulmonary function tests without identifiable risk factors (e.g., cigarette smoking, occupational exposure).
    d. For individuals 18 years or older with necrotizing panniculitis.
    e. For the siblings of an individual with known alpha-1 antitrypsin (AAT) deficiency.
    f. For individuals with anti-proteinase three-positive vasculitis (C-ANCA [anti-neutrophil cytoplasmic antibody]-positive vasculitis).

g. For individuals with bronchiectasis without evident etiology.
h. For individuals with neonatal cholestasis.

2. For individuals who have negative genotype results for common variants or who have discordant results between AAT serum levels and proteotype, but for whom a clinical suspicion of AAT deficiency remains, isoelectric focusing/phenotyping is considered **reimbursable**.

The following is **not reimbursable** due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual's illness.

3. For all other situations not described above, testing for AAT deficiency is **not reimbursable**.

Coding

Code	Description
CPT	
82103	Alpha-1-antitrypsin; total
82104	Alpha-1-antitrypsin; phenotype

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

Notes

Note 1

Alpha-1 antitrypsin (AAT) phenotyping should be performed using isoelectric focusing. AAT proteotyping (Pi-typing or protease inhibitor typing) for Z and S alleles should be performed using liquid chromatography-tandem mass spectrometry.

Table of Terminology

Term	Definition
A1AT	Alpha-1 antitrypsin

Term	Definition
AAT	Aspartate aminotransferase
AATD	Alpha 1-antitrypsin deficiency
ACG	American College of Gastroenterology
ALT	Alanine transaminase
AST	Aspartate aminotransferase
ATS/ERS	American Thoracic Society/European Respiratory Society
C-ANCA	C-Anti-neutrophil cytoplasmic antibody
CMS	Centers for Medicare and Medicaid Services
COPD	Chronic obstructive pulmonary disorder
CTS	Canadian Thoracic Society
ERS	European Respiratory Society
GC	Gas chromatography
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HPLC	High-performance liquid chromatography
LBV	Likely benign variants
LDTs	Laboratory developed tests
MALDI	Matrix-assisted laser desorption ionisation
MMP-12	*Matrix metalloproteinase-12* gene
MS-TOF	Time of flight mass spectrometry
NAFLD	Non-alcoholic fatty liver disease
NICE	National Institute Health and Care Excellence
NORD	National Organization for Rare Disorders
ON-CD	Ontario Center
PCR	Polymerase chain reaction
Pi	Protease inhibitor
PiMZ	Protease inhibitor Z allele
PV	Pathogenic variant
QTOF	Quadrupole time of flight
RCTs	Randomized controlled trials
RFLP	Restriction fragment length polymorphism

Term	Definition
SERPINA1	Serine protease inhibitor
UMV	Undefined molecular variants
WHO	World Health Organization

Evidence Review

Scientific Background

Alpha-1 antitrypsin deficiency (AATD) 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 (Stoller & Aboussouan, 2012). It is estimated (Campos et al., 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 et al., 2007), but most current estimates are that three million people worldwide have severe AATD (Stoller, 2023).

Alpha-1 antitrypsin deficiency 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* (Stoller, 2023).

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 (Stoller, 2023, 2024).

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. 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 (Stoller, 2024). AATD is a common genetic cause of liver disease in children (de Serres et al., 2003).

Skin manifestations of AATD are also recognized. The most 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 (Stoller, 2024).

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 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 (Stoller, 2023).

Laboratory testing for AATD is comprised of three strategies: serum or plasma AAT quantification, AAT protein phenotyping, and genotyping. Guidelines from national and international societies (e.g., World Health Organization, Spanish Society of Pneumology and Thoracic Surgery, European Respiratory Society) recommend testing for AATD at least once per lifetime for all individuals with liver disease of unknown etiology and for all individuals with chronic obstructive pulmonary disorder (COPD), emphysema, or adults with asthma and irreversible airflow obstruction (Belmonte et al., 2020).

Proprietary Testing

Initial testing often begins with serum quantification of AAT protein. This can be done through several methods, including immune turbidimetry and nephelometry (Stoller, 2023). 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 (Stoller, 2023).

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 (Stoller, 2023).

In 2017, Grifols won FDA approval for AAT Deficiency Test, which is capable of simultaneously analyzing 99% of the most prevalent known mutations causing alpha-1 antitrypsin deficiency. The molecular test analyzes simultaneously 192 samples per kit, and in a single reaction, identifies 14 of the most prevalent known mutations in the SERPINA1 gene, responsible for this genetic disorder (Grifols, 2017).

Using Progenika's FDA-cleared A1AT Genotyping Test, Matrix Clinical Labs released the proprietary Alpha ID screening test, a comprehensive targeted genetic test assessing 14 common and rare alleles in the *SERPINA1* gene. The Alpha ID screening test utilizes a noninvasive cheek swab screen. If a positive result is found using this test, a follow-up test, Alpha ID Confirm, uses a finger stick and a blood spot card to asses A1AT protein levels as well a potential reflex to next-generation sequencing (NGS) to help physicians achieve an accurate diagnosis of Alpha-1 antitrypsin deficiency (A1ATD) (AlphaID, 2024).

Clinical Utility and Validity

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 (GOLD, 2024) 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 COPD. In addition, several studies have documented that the disease is under-recognized with delay in diagnosis of between five to eight years (Barrecheguren et al., 2016; Stoller et al., 2005).

Snyder et al. (2006) 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, seven were attributed to phenotyping errors. Four percent 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. (2015) examined a cohort of COPD patients and the prevalence of severe AATD. A total of 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 three were SZ. Of the 202 other patients, 29 were a Z heterozygote, 25 were an S heterozygote, and four were an SS homozygote. Lastly, 144 patients could not be definitively diagnosed (Sorroche et al., 2015).

Corda et al. (2011) examined the prevalence of AATD in a supposed "high-risk" area. A total of 817 residents participated, and 67 had low AAT serum levels. Overall, 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 et al. (2018) 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. (2016) 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. Overall, 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).

Mattman et al. (2020) compared the comprehensiveness and efficiency of pathogenic variant (PV) detection of four different protocols from 2011 to 2018 in laboratories across Canada. From 5399 index patients, 396 ZZ genotypes were identified. The protocol for serum A1AT concentration/DNA sequencing in the Ontario center (ON-CD) yielded the highest PV detection – "genotypes with at least one PV, other than S, Z, or F, were identified at 0.67/ZZ as compared to <0.2/ZZ (all others)." However, it also had the highest rates of undefined molecular variants (UMV) (0.16/ZZ vs <0.12/ZZ) or likely benign variants (LBV) compared to all others (0.08/ZZ vs <0.06/ZZ). The authors concluded the "strategies with readily detect variants across the full

coding sequence of *SERPINA1* detect more PV as well as more UMV and LBV" (Mattman et al., 2020).

Hamesch et al. (2019) evaluated the clinical landscape of liver symptoms in patients with AATD, specifically the Pi*ZZ genotype. A total of 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 ≥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 liquid. 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. (2019) 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 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).

Carreto et al. (2020) examined the utility of routine screening for AATD among patients with bronchiectasis, due to the contradiction in guidelines from the British Thoracic Society, which recommend screening for bronchiectasis among patients with AATD, but not vice versa. After screening 1600 patients with bronchiectasis from two centers in the UK from 2012-2016, they found only eight patients with AATD. They concluded that because of the low prevalence of AATD as an etiology for disease presentation among patients with bronchiectasis, routine screening for AATD would not significantly impact clinical management through augmentation therapy, smoking cessation, and genetic counselling, among other methods. Despite this, the

researchers did note that higher rates of detection may be found in other geographical regions in the UK or in other countries (Carreto et al., 2020).

In 2021, Murray et al. evaluated the efficacy of a liquid chromatography-tandem mass spectrometry (LC-MS/MS) (proteotyping)-based algorithm for AATD detection (n=5474), as compared to the more traditional isoelectric focusing (IEF) phenotyping (n=16147). Here, the authors found that LC-MS/MS reduced the rate of IEF) phenotyping by 97% and the 3% of cases that were reflexed to IEF resulted in and addition 0.2% of phenotype findings. By retrospectively applying the proteotype-based algorithm to the IEF cohort, they demonstrated a 99.9% sensitivity for the detection of deficiency-associated phenotypes. The authors concluded that the "proteotype algorithm is a sensitive and cost-effective approach for the diagnosis of clinical AAT deficiency" (Murray et al., 2021).

Bellemare et al. (2021) studied the clinical utility of determining the allelic background of mutations causing alpha-1 antitrypsin deficiency. *SERPINA1* was DNA sequenced to identify rare variants that could confer the risk of developing emphysema. Seven carriers of a rare variant, Leu353Phe_fsTer24, known to lead to undetectable serum levels of AAT, were studied using an allele-specific DNA sequencing method that they developed. Results demonstrated that Leu353Phe_fsTer24 variant was transmitted on the same allele as the M3 variant in all the patients and two of the seven patients had either a S or Z allele. The lowest AAT serum levels were observed in compound heterozygotes for the S or Z allele, suggesting higher risk of developing emphysema. This study showed that understanding the clinical significance of genetic variants found in SERPINA1 can lead to better clinical outcomes (Bellemare et al., 2021).

Ashenhurst et al. (2022) conducted a study to examine whether direct-to-consumer genetic testing increased the identification of previously undetected individuals specifically with AATD, and whether it impacted clinical care. In this cross-sectional study using a survey from the 23andMe, Inc. research platform with 195,014 participants, researchers found that the allele frequency of PI*S was 15.1%, 6.5% for PI*Z, and 0.63% with PI*ZZ. Half of those with the PI*ZZ allele combination were able to confirm their diagnosis with a physician. Twenty seven percent of the participants were first made aware of their disease status through this test, and among these participants, "the diagnostic delay interval was 22.3 years." As a result of this finding, there was a 1.7 times increased odds of reporting smoking reduction and 4.0 times increased odds of reporting reduced alcohol consumption. This demonstrates that having convenient methods of detecting pathogenic variants of the *SERPINA1* gene in commercial testing could benefit patients in the long run in terms of reducing risks of complications from AATD (Ashenhurst et al., 2022).

Balcar et al. (2022) studied the association between the alpha-1 antitrypsin Pi∗Z allele and liver disease. The study included 1118 patients with advanced chronic liver disease, all of whom had undergone genotyping for the Pi*Z/Pi*S allele. Compared to non-carriers, Pi∗Z carriers had more

severe portal hypertension and hepatic dysfunction. “Harbouring the Pi∗Z allele was significantly associated with an increased probability of liver transplantation/liver-related death,” but “the Pi∗S allele was unrelated to liver disease severity” and “Pi∗S carriers had no increased risk of events.” The authors concluded that “genotyping for the Pi∗Z allele identifies patients with ACLD at increased risk of adverse liver-related outcomes, thereby improving prognostication” (Balcar et al., 2022).

Clark et al. (2018) studied the clinical and histologic features of individuals with AATD. The study included 94 non-cirrhotic adults with Pi*ZZ AATD. “The prevalence of clinically significant liver fibrosis (F ≥ 2) was 35.1%. Alanine aminotransferase, aspartate aminotransferase and gamma-glutamyltransferase values were higher in the F ≥ 2 group.” Metabolic syndrome, the presence of accumulated abnormal AAT in hepatocytes, portal inflammation, and hepatocellular degeneration were all associated with clinically significant fibrosis. The authors concluded that “over one-third of asymptomatic and lung affected adults with 'PI*ZZ' AATD have significant underlying liver fibrosis” and that “liver disease in this genetic condition may be related to a "toxic gain of function" from accumulation of AAT in hepatocytes” (Clark et al., 2018).

Eriksson et al. (1986) studied the association between AATD and cirrhosis and primary liver cancer. The study included 17 autopsy cases of individuals with AATD. Each autopsy was matched with four control cases. “The results indicated a strong relation between alpha 1-antitrypsin deficiency and cirrhosis and primary liver cancer” (Eriksson et al., 1986).

Fromme et al. (2022) studied the association between AATD and hepatobiliary phenotypes. The study included 1104 participants (586 Pi*ZZ, 239 Pi*SZ, 279 non-carriers). “Pi*ZZ individuals displayed the highest liver enzyme values, the highest occurrence of liver fibrosis/cirrhosis and primary liver cancer… Pi*SZ participants displayed higher liver enzymes, more frequent liver fibrosis/cirrhosis… Subjects with Pi*MZ genotype had slightly elevated liver enzymes and moderately increased odds for liver fibrosis/cirrhosis…Individuals with homozygous Pi*S mutation (Pi*SS genotype) harboured minimally elevated alanine aminotransferase values.” The authors concluded that their findings classify hepatobiliary phenotypes with their most relevant AATD genotypes (Fromme et al., 2022).

The Childhood Liver Disease Research Network Longitudinal Observational Study of Genetic Causes of Intrahepatic Cholestasis (Teckman et al., 2020) is a longitudinal study about pediatric cholestatic liver disease. The study included 350 participants ages zero to 25 with native livers. Overall, 18 participants developed hypertension, and two died, but “there was no difference in participants with or without preceding neonatal cholestasis progressing to transplantation or death during the study, or in experiencing portal hypertension.” The authors concluded that, in youth with AATD, “progression to liver transplantation is slow and death is rare, but the risk of complications and severe liver disease progression persists throughout childhood.” The authors also note that “A history of neonatal cholestasis is a weak predictor of severe disease” (Teckman

et al., 2020). Teckman et al. (2023) then focused on neonatal cholestasis in children with AATD, using two subgroups: participants with neonatal cholestasis (n=46), and all participants who progressed to livre transplant (n=119). The authors reported "an association of neonatal gamma-glutamyl transpeptidase elevation to more severe disease, and a higher rate of neonatal cholestasis progression to portal hypertension than previously reported (41%) occurring at median age of 5 months." All participants, regardless of neonatal cholestasis, were at risk of progression to liver transplant, but of the participants that progressed to liver transplant, those with neonatal cholestasis were significantly younger at transplant than those without neonatal cholestasis. The authors further concluded that "patients with AATD and neonatal cholestasis are at risk of early progression to severe liver disease, but the risk of severe disease extends throughout childhood" (Teckman et al., 2023).

Lin et al. (2019) completed a systematic literature review of AATD deficiency-associated liver disease in children and put together diagnostic testing recommendations. The literature review revealed that "liver disease occurs in 10% of children, manifested by cholestasis, pruritus, poor feeding, hepatomegaly, and splenomegaly, but the presentation is highly variable." The authors recommend genetic testing for AATD in children with unexplained liver disease or suspected AATD, noting "consensus guidelines recommend diagnostic testing for all patients who have unexplained liver disease" (level of evidence for recommendations: A, based on consistent and good quality patient-oriented evidence) (Lin et al., 2019).

Guidelines and Recommendations

American Thoracic Society/European Respiratory Society (ATS/ERS)

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:

- Symptomatic adults with emphysema, COPD or asthma with airflow obstruction that is not completely reversible with aggressive treatment with bronchodilators

- Individuals with unexplained liver disease, including neonates, children, and adults, particularly the elderly
- Asymptomatic individuals with persistent obstruction on pulmonary function tests with identifiable risk factors (e.g., cigarette smoking, occupational exposure)
- Adults with necrotizing panniculitis
- Siblings of an individual with known alpha-1 antitrypsin (AAT) deficiency

Type B recommendations for diagnostic testing in the following situations:

- Adults with bronchiectasis without evidence etiology
- Adolescents with persistent airflow obstruction
- Asymptomatic individuals with persistent airflow obstruction and no risk factors
- Adults with C-ANCA positive (anti-proteinase 3-positive) vasculitis
- Individuals with a family history of COPD or liver disease not known to be attributed to AAT deficiency
- Distant relatives of an individual who is homozygous for AAT deficiency
- Offspring or parents of an individual with homozygous AAT deficiency
- Siblings, offspring, parents or distant relatives of an individual who is heterozygous for AAT deficiency
- Individuals at high risk of having AAT deficiency-related diseases
- Individuals who are not at risk themselves of having AAT deficiency but who are partners of individuals who are homozygous or heterozygous for AAT deficiency

Type C recommendations for diagnostic testing in the following situations:

- Adults with asthma in whom airflow obstruction is completely reversible
- Predispositional testing
- Population screening of smokers with normal spirometry

Type D recommendations for diagnostic testing in the following situations:

- Predispositional fetal testing
- 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).

The ATS/ERS states that "Regarding hepatic presentations of AAT deficiency later in childhood, during adolescence, and in adulthood, reports indicate that patients may present with hepatosplenomegaly, ascites, upper gastrointestinal bleeding resulting from esophageal varices, chronic hepatitis, cirrhosis, or hepatic failure. The presentation of AAT deficiency may appear similar to other chronic liver diseases, including autoimmune hepatitis, drug-induced hepatitis, chronic viral hepatitis, and Wilson's disease. The weight of these reports suggests that patients with any unexplained features of chronic liver disease should be evaluated for AAT deficiency" (ATS/ERS, 2003).

American College of Gastroenterology (ACG)

The ACG notes that "defective production of the alpha-1 anti-trypsin protein may result in both panacinar emphysema and chronic obstructive pulmonary disease, as well as progressive liver disease, liver cirrhosis, and hepatocellular carcinoma" and 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 anti-trypsin 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 et al., 2017).

National Organization for Rare Disorders

NORD publishes information on multiple rare disorders that may otherwise lack national guidelines and recommendations. One such disorder is neonatal cholestasis, which refers to impaired flow of bile from the liver cells into the intestine of a newborn. While neonatal cholestasis may be caused by viruses, metabolic disease, or rare disease that affect or impair the function of the liver, it can also be caused by genetic disorders. "The incidence of neonatal cholestasis is estimated to be ~1:2500 live births worldwide, and 25% to 50% are now known to be associated with changes (variants or mutations) in specific genes" (NORD, 2024b). These genetic disorders include "alpha-1-antitrypsin deficiency, PFIC and Alagille syndrome" (NORD, 2024b).

World Health Organization (WHO)

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)

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

- "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" (Miravitlles et al., 2017).

Alpha-1 Foundation

The Alpha-1 Foundation (Sandhaus et al., 2016) sponsored a medical and scientific advisory committee of experts to examine all relevant, recent literature 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" (Sandhaus et al., 2016).

Global Initiative for Chronic Obstructive Lung Disease (GOLD)

The GOLD guideline notes that "The most relevant (albeit rare) genetic risk factor for COPD identified to date are mutations in *SERPINA1* gene leading to α-1 antitrypsin deficiency. A number of other genetic variables have also been associated with reduced lung function and risk of COPD, but their individual effect size is small."(GOLD, 2024).

Canadian Thoracic Society (CTS)

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

- "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)

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" (NICE, 2019).

Government of British Columbia

The British Columbia guidelines on the diagnosis and management of COPD state that, "testing for A1AT deficiency is expensive, low yield, often duplicated and may not alter management in a meaningful way. Therefore, refer patients with high pre-test probability to a specialist" (BC Guidelines, 2024).

US Food and Drug Administration (FDA)

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 November 7, 2019, the FDA approved Grifols' AlphaID, a cheek swab that can screen patients with COPD for alpha-1 antitrypsin deficiency. It "utilizes an FDA-approved genotyping assay to screen for the 14 most prevalently reported genetic mutations associated with Alpha-1, including the S, Z, F, I alleles, as well as rare and null alleles, helping detect patients who are at risk for this treatable condition" (Grifols, 2019).

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.

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). LDTs are not approved or cleared by the US Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

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History

Date	Comments
11/01/25	New policy, approved October 14, 2025, effective for dates of service on or after February 6, 2026, following 90-day provider notification. Add to Routine Test Management Policy section. Serum quantification and phenotyping or proteotyping for alpha-1 antitrypsin deficiency may be considered reimbursable once per lifetime when clinical criteria outlined in this policy are met, including specific symptoms, risk factors, or family history.

Scope: Medical policies for routine test management are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices and reimbursement methodology. Coverage and reimbursement for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.