I. POLICY

Genetic testing for alpha-1 antitrypsin (AAT) deficiency may be considered medically necessary when both 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 AAT deficiency. (See Guidelines) AND
2. Patient has a serum alpha-1 antitrypsin level in the range of severe deficiency (See Guidelines)

Genetic testing for alpha-1 antitrypsin deficiency is considered investigational in all other situations. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

Policy Guidelines

According to the 2003 joint statement on diagnosis and management of alpha-1 antitrypsin deficiency by the American Thoracic Society/European Respiratory Society:

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

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

The most common abnormal forms are the Z allele and the S allele. Individuals with 2 copies of the Z allele (ZZ) tend to be most severely affected, with mean serum concentrations of AAT of 2.5 to 7 umol/L and a high risk of COPD.

Cross-reference:
MP-2.169 Alpha Proteinase Inhibitors (Human) (Aralast®, Aralast np®, Glassia™, Prolastin-C®, Zemaira®)

II. PRODUCT VARIATIONS

[N] = No product variation, policy applies as stated
[Y] = Standard product coverage varies from application of this policy, see below

[N] Capital Cares 4 Kids   [N] Indemnity
[N] PPO                   [N] SpecialCare
[N] HMO                   [N] POS
[N] SeniorBlue HMO        [Y] FEP PPO*
[N] SeniorBlue PPO

*Refer to FEP Medical Policy Manual MP-2.04.79 Genetic Testing for Alpha-1 Antitrypsin deficiency. The FEP Medical Policy manual can be found at: www.fepblue.org
Alpha-1 antitrypsin deficiency (AATD) is an autosomal recessive genetic disorder that results in decreased production of the alpha-1 antitrypsin (AAT) protein, or production of abnormal types of the protein that are functionally deficient. Individuals with AATD, especially smokers, have an increased risk of lung and liver disease. Tests are available to measure serum AAT levels and for AAT protein variant phenotyping. Genetic testing is also available to detect the most common mutations associated with AATD.

Alpha-1 antitrypsin deficiency (AATD) is an autosomal recessive genetic disorder that results in decreased production of the alpha-1 antitrypsin (AAT) protein, or production of abnormal types of the protein that are functionally deficient. Data from screening studies have found the prevalence of AATD in the United States to be between 1 in 2,857 and 1 in 5,097 individuals respectively. (1) AAT is an acute phase glycoprotein, synthesized primarily 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 but can also break down and damage lung tissue if its action is not regulated by AAT. Individuals with AAT deficiency thus have an increased risk of lung disease.

Respiratory disease tends to be more severe and occur sooner (i.e., between age 40 and 50) in individuals with AAT deficiency who smoke cigarettes and/or are exposed to occupational dust or fumes. In non-smokers and individuals without environmental exposure, onset of respiratory disease occurs more commonly in the sixth decade. Childhood-onset lung disease is rare with AATD. AATD is also associated with an increased risk of liver disease, thought to occur due to aggregation of damaged AAT in the liver cells, where the protein is produced. The most common manifestation of liver disease in childhood is jaundice. Adult-onset liver disease generally manifests as cirrhosis and fibrosis. Necrotizing panniculitis is a rare, but well-recognized complication of AAT deficiency. This dermatological condition is characterized by inflammatory and necrotizing lesions of the skin and subcutaneous tissue.

The primary interventions to prevent or treat symptoms in individuals 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 mutations in the lungs e.g., cigarette smoke, dust and workplace chemicals, as well as substances such as alcohol that can cause liver damage. There are also general recommendations to exercise, avoid stress and have a nutritious diet. Furthermore, patients with AATD may be recommended to have earlier or more aggressive treatments for conditions such as asthma outbreaks or acute exacerbations of chronic obstructive pulmonary disease (COPD). One treatment option that is specific to AATD is alpha-1 antitrypsin
augmentation. Patients generally receive injections of plasma every 3 to 4 weeks for life. There is a lack of consensus about the efficacy of this treatment.

Diagnostic testing for AAT

Several types of tests are available for patients who are suspected of having AATD. A blood test is available that quantifies the total amount of alpha-1 antitrypsin 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 AAT deficiency. In general, a serum concentration of AAT less than 15-20% of the normal value is highly suggestive of a homozygous alpha-1 antitrypsin mutation. (4)

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 to normal patterns to determine if and what type of abnormal AAT protein may be present.

Genetic testing is also available. Production of AAT is encoded by the SERPINA1 gene which is co-dominant (each gene copy is responsible for producing half of the AAT). Although there are more than 75 sequence variants of the SERPINA1 gene (i.e., 75 possible alleles), only several are common in North America. Approximately 95% of individuals have 2 copies of the normal M allele sequence (MM) and have mean serum concentrations of AAT ranging from 20-53 umol/L. The most common abnormal forms are the Z allele and the S allele. Individuals with 2 copies of the Z allele (ZZ) tend to be most severely affected, with mean serum concentrations of AAT of 2.5 to 7 umol/L and a high risk of COPD. Individuals with genotype SS and heterozygous individuals with genotype MZ have low risk of COPD and moderately lower levels of AAT. Individuals with rarer mutations of the SERPINA1 gene or null alleles may not produce any AAT and are also at high risk.

Genetic testing for AATD is most commonly done by the alpha-1 genotype test. This test uses Polymerase chain reaction (PCR) analysis, or some other type of nucleic acid-based analysis, to identify abnormal alleles of AAT DNA. Currently, genotype tests are only designed to detect the most common mutations i.e. the S and Z alleles.

A common approach to testing for AATD is to initially perform serum quantitation. If the AAT level is found to be low, a follow-up phenotype or genotype test is ordered. Another approach, as exemplified by the Mayo clinic, is to perform serum protein quantification, followed by genotype testing in individuals with clinical suspicion of AATD. If these tests are discordant, phenotype testing is then performed.

**Regulatory Status**

An example of a U.S. Food and Drug Administration (FDA)-cleared phenotyping test is the Hydragel 18 alpha-1 antitrypsin isofocusing kit (Sebia Inc., GA). In 2007, this test was cleared
for marketing through the 510(k) process. The test is designed for the qualitative detection and identification of the phenotypes of AAT protein.

No FDA-cleared genotyping tests were found. Thus, genotyping is offered as a laboratory-developed test. Clinical laboratories may develop and validate tests in-house (“home-brew”) and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The laboratory offering the service must be licensed by CLIA for high-complexity testing.

IV. RATIONALE

Validation of the clinical use of any genetic test focuses on 3 main principles: (1) analytic validity, which refers to the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent; (2) clinical validity, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and (3) clinical utility, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

Analytic validity

Analytic performance of the Hydrogel AAT phenotyping test is reported in a U.S. Food and Drug Administration (FDA) decision summary document. (7) Within-run test result reproducibility was determined by testing 8 samples 15 or 18 times on a single gel. Two normal samples and 6 pathological samples with MS, SS, MZ, ZZ and MX phenotypes were included; the test was able to reproduce the corresponding phenotype correctly. Between-run gel reproducibility was determined by testing 15 samples and 3 controls 12 times on 2 lots of gels. Again, the phenotypes were reproduced correctly.

No published studies on the analytic validity of any alpha-1 antitrypsin (AAT) genotyping test conducted in the United States, other than FDA documents, were identified.

Clinical validity

In 2008, Ljujic et al in Serbia published findings of a study with 27 emphysema patients. (8) Phenotyping was performed using isoelectric focusing and genotyping by denaturing gradient gel electrophoresis. Isoelectric focusing was successfully performed in 25 cases and genotyping results were available for all 27 patients. Phenotyping and genotyping were concordant for the 4 patients found to have 1 or 2 “Z” alleles. However, genotyping found 2 unusual mutations and in both of these cases, phenotyping found normal variants.
MEDICAL POLICY

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The FDA decision summary for the hydrogel phenotyping test included an evaluation of clinical sensitivity and specificity. (7) Samples were evaluated from 64 patients with the following diagnoses: congenital alpha-1 antitrypsin deficiency (AATD) (n=16), pulmonary disorder (n=15), hepatic disorder (n=8), infertility (n=1), panniculitis (n=1), and normal (n=23). The sensitivity of the phenotype test was 39 of 39 (100%) and the specificity was 23 of 25 (92%). (Note: This analysis excludes 4 individuals with indeterminate diagnoses).

Clinical utility

The clinical utility of genetic testing for AATD depends on how the results can be used to improve patient management. With AATD, this could occur in several ways, including the following:

- Patient knowledge of AAT status could lead to behavior change that improves health outcomes. In particular, asymptomatic smokers could quit smoking, which prevents or delays onset of lung disease, and symptomatic smokers could quit smoking, which might prevent progression of lung disease. Knowledge of AAT status could also lead to other behavioral changes including avoiding pollutants, increasing exercise, avoiding alcohol, and avoiding smoking for those who have not started.(9)

- A diagnosis of AATD could lead to changes in treatment, which may improve patient outcomes. The only treatment specific to AATD is AAT augmentation therapy. In addition, the intensity and/or timing of other treatments may be different for patients with known AATD. This includes antibiotic treatments for lung infections and vaccinations (influenza, pneumococcus, hepatitis A and B).(1)

Smoking cessation

In 2003, a joint statement on diagnosis and management of AATD from the American Thoracic Society (ATS) and the European Respiratory Society (ERS) was published. (1) The authors stated that the joint statement was based on systematic reviews and an evidence-based approach to evaluating evidence. A review of smoking cessation studies in the ATS/ERS joint statement did not identify any randomized controlled trials (RCTs) on the impact of AATD status on smoking cessation. However, they identified an RCT on a related topic. This study which found that, at 1 year, patients who received genetic susceptibility information (in this case, CYP2D6 genotype results) were significantly more likely to report a quit attempt than individuals who received counseling only; quit rates did not differ significantly in the 2 groups.(10)

In 2007, Carpenter et al reported on findings of a survey of subjects who had volunteered for genetic testing for AATD. (11) A total of 4344 individuals completed a test kit; 331 (7.6%) respondents were rejected because their blood sample was insufficient. The remaining participants were mailed a follow-up letter with their test results and a genotype-specific
The testing revealed that 2228 (56%) of the valid samples tested normal, 1530 (38%) were found to be heterozygous carriers for AATD (MZ genotype), and 255 (6%) were found to be severely AAT deficient (SZ or ZZ genotype). A total of 729/2,228 (33%) of participants with valid blood samples identified themselves as current cigarette smokers. These smokers were sent an additional questionnaire 3 months after the initial letter. Test results among smokers were 55% normal genotype, 38% carrier, and 7% severely AAT deficient. Of the 729 surveys sent to smokers, 205 (28%) were completed. Six smokers were excluded because they smoked less than 6 cigarettes per day, leaving 199 participants in the study sample. Survey responders were more likely to be older than nonresponders; there were no significant differences in response rates by genotype group. Among survey respondents, individuals with severe AATD were significantly more likely to make any self-reported quit attempt than were individuals with a normal genotype (59% vs 33%, p<0.05). Of 8 quit behaviors listed in the survey, AAT deficient smokers reported engaging in a mean of 2.4 (SD=2.3). This was significantly higher than the number of quit behaviors reported by carriers (0.7, SD=1.3) or normals (1.3, SD=2.0; p=0.04). There was not a significant difference between groups, however, in the abstinence rate at 3 months (defined as 24-hour point prevalence). This study was limited in that it lacked a control group of smokers who were not tested for AATD, and there was a low response rate to the 3-month survey.

**Smoking prevention**

The ATS/ERS joint statement on AATD identified 2 case-control studies that included children identified at birth as having AATD and matched to a demographically similar control group. The number of children with AATD was 61 in 1 study and 22 in the other. These studies reported a lower frequency of adolescent smoking in individuals identified at birth as having AAT deficiency, compared with the control individuals.(1)

**Section summary**

The available studies suggest that knowledge of AATD status may lead to more quit attempts but not higher smoking cessation rates. There is also limited evidence from 2 small case-control studies that individuals who know from birth they have AATD are less likely to initiate smoking than individuals without genetic information knowledge.

**Treatments for individuals with AATD**

*Alteration of timing or intensity of treatments for patients with AATD*

The ATS/ERS joint statement on AATD (1) recommended the following interventions for patients with emphysema who have AATD:
Inhaled bronchodilators
- Preventive vaccinations against influenza and pneumococcus
- Supplemental oxygen when indicated by conventional criteria, including during air travel
- Pulmonary rehabilitation for individuals with functional impairment
- Consideration of lung transplantation for selected individuals with severe functional impairment and airflow obstruction
- Early antibiotic treatment for individuals with purulent acute exacerbations of chronic obstructive pulmonary disease (COPD).

The authors noted that these are recommendations for treating patients with COPD in general and are applicable to those with pulmonary disease associated with AATD; no controlled studies specific to AATD were cited in support of the previous recommendations to determine whether the timing, intensity, or compliance with these treatments is altered by knowledge of AATD status.

**AAT augmentation therapy**

A 2010 Cochrane review addressed the benefits and harms of augmentation therapy with AAT in patients with AATD and lung disease. (12) The investigators searched for RCTs comparing augmentation therapy with AAT to placebo or no intervention and reporting 1 or more of the primary outcomes: mortality, forced expiratory volume in 1 second (FEV1) or adverse effects. Two RCTs were identified; both were conducted by the same research team. (13, 14) The first trial, published in 1999, enrolled 58 ex-smokers with AATD (ZZ genotype). Patients were treated with AAT (250 mg/kg) or placebo 4 times a week for 3 years. The primary outcome was FEV1. The second trial, published in 2009, included 82 ex-smokers or never smokers with the ZZ or heterozygous Z genotype. Patients were treated for 2 years with AAT (60 mg/kg) or placebo. The primary outcome was lung density measured by computed tomography (CT) scans, which the trial authors noted was an exploratory outcome; in the trial, FEV1 was reported as a secondary outcome. Adverse events were not reported in the first trial. A pooled analysis of the 2 studies did not find a significant difference in FEV1 deterioration over the course of the study in the treatment compared with the placebo group. The pooled mean difference in FEV1 (mL) was -19.92 (95% confidence interval [CI], -40.86 to 1.02). A pooled analysis of lung density change (g/L) according to CT findings favored the treatment group. The mean difference was 1.14 (95% CI, 0.14 to 2.14; p=0.026). Potential biases in the trials noted by the Cochrane review authors include potential financial conflicts of interest and, in the second trial, selective reporting of outcomes, which refers to the trial authors’ emphasis of the intermediate outcome CT lung density. The Cochrane review concluded that there was insufficient evidence to recommend augmentation therapy with AAT.

No additional RCTs evaluating the impact of AAT augmentation therapy on health outcomes in patients with AATD have been published since the 2010 Cochrane review.
Section summary

A U.S. national guideline recommends different interventions for individuals with emphysema found to have AATD such as preventive vaccinations and early antibiotic treatment. The only AATD-specific treatment is AAT augmentation therapy, which is often prescribed for patients with documented AATD and COPD. A Cochrane review concluded that the RCT evidence was insufficient to determine whether AAT augmentation therapy is effective for improving health outcomes in patients with AATD. In their pooled analysis of data from 2 studies, there was significantly greater decrease in lung density among patients who received augmentation therapy; the difference in FEV\textsubscript{1} was not statistically significant although the upper CI was close to 1.

Ongoing Clinical Trials

International Study Evaluating the Safety and Efficacy of Inhaled, Human, Alpha-1 Antitrypsin (AAT) in Alpha-1 Antitrypsin Deficient Patients With Emphysema (NCT01217671)(15): This is a double-blind RCT that compares the safety and efficacy of inhaled AAT versus placebo in adults with emphysema. Estimated enrollment is 200 patients. The primary efficacy measures are exacerbations and lung density after 1 year. Adverse events are included as secondary outcomes. The study is being conducted at sites in Canada and several European countries and is sponsored by Kameda Ltd.

Summary

The literature on the analytic and clinical validity of genetic testing for alpha-1 antitrypsin deficiency (AATD) is limited. In addition, there are few randomized controlled trials (RCTs) evaluating the impact of AATD testing on patient outcomes. However, national guidelines recommend specific interventions for patients with emphysema and AATD, and alpha-1 antitrypsin (AAT) augmentation therapy is often prescribed for patients with AATD and chronic obstructive pulmonary disorder (COPD). The available evidence suggests that knowledge of AATD status may discourage nonsmokers from initiating smoking and may increase quit attempts among smokers, but it has not been shown to increase successful quitting. Evidence from small RCTs on AAT augmentation therapy are not definitive of a treatment benefit, but reports trend toward improvement in lung function. As a result, genetic testing for AATD may lead to improved outcomes by altering interventions for AATD and therefore may be considered medically necessary for individuals with suspected AATD or those at high risk for AATD due to personal or family history who have serum levels of AAT level in the range for homozygous disease.
Practice Guidelines and Position Statements

In 2012, the Canadian Thoracic Society published a clinical practice guideline on AAT deficiency testing and augmentation therapy. (16) The recommendations regarding targeted testing for AATD are:

- Targeted testing for AAT deficiency may be considered in those individuals with 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 AAT deficiency is not recommended in individuals with bronchiectasis or asthma.

In 2003, the American Thoracic Society published recommendations on the diagnosis and management of individuals with AAT deficiency. (1)

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
- 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 3 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.

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers

V. DEFINITIONS

N/A

VI. BENEFIT VARIATIONS

The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based in all cases on the
applicable contract language. Medical policies do not constitute a description of benefits. A member’s individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member’s benefit information or contact Capital for benefit information.

VII. DISCLAIMER

Capital’s medical policies are developed to assist in administering a member’s benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member’s benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

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<tr>
<th>ICD-9-CM Diagnosis Code*</th>
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<td>ALPHA-1-ANTITRYPSIN</td>
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*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.
The following ICD-10 diagnosis codes will be effective October 1, 2015:

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<th>ICD-10-CM Diagnosis Code*</th>
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IX. REFERENCES


X. POLICY HISTORY

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<td>CAC 4/24/12 New policy. Adopt BCBSA. Genetic testing for AATD may be considered medically necessary for individuals who meet criteria and investigational otherwise.</td>
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<tr>
<td></td>
<td>CAC 7/22/14 Consensus review. Rationale updated. No changes to references or policy statements.</td>
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Health care benefit programs issued or administered by Capital BlueCross and/or its subsidiaries, Capital Advantage Insurance Company®, Capital Advantage Assurance Company® and Keystone Health Plan® Central. Independent licensees of the BlueCross BlueShield Association. Communications issued by Capital BlueCross in its capacity as administrator of programs and provider relations for all companies.