Genetic Testing for Alpha-1 Antitrypsin Deficiency

Description of Procedure or Service

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.

Description of Disease

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.

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.

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

Pulmonary Manifestations

Respiratory disease tends to be more severe and occur sooner (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 toxic gain-of-function, leading to an aggregation of damaged AAT in the liver cells, where the protein is produced. The most common manifestation of liver disease in childhood is jaundice.

Liver Manifestations

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

Clinical Management
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 addition, individuals with AATD are advised to avoid other substances than can irritate 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-1antitrypsin augmentation. Patients generally receive injections of plasma every 3 to 4 weeks for life. Inhaled AAT augmentation therapy is under development. There is a lack of consensus about the efficacy of this treatment. Product labels state that the effect of augmentation therapy on emphysema progression and pulmonary exacerbations has not been demonstrated in randomized controlled trials.

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

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.

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 two 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.
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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**

In 2007, the phenotyping test Hydragel 18 A1AT ISOFOCUSING kit (Sebia, GA) was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process for qualitative detection and identification of the phenotypes of alpha1-antitrypsin protein.

Clinical laboratories may develop and validate tests in-house (“home-brew”) and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). The laboratory offering the service must be licensed by CLIA for high-complexity testing. Molecular diagnostic laboratories may also be accredited by the College of American Pathologist Laboratory Accreditation Program.

***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**

BCBSNC will provide coverage for genetic 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**

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 Genetic Testing for Alpha-1 Antitrypsin Deficiency is covered**

Genetic testing for alpha-1 antitrypsin 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 Policy Guidelines); **AND**

2. Patient has a serum alpha-1 antitrypsin level in the range of severe deficiency (see Policy Guidelines).

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

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

**Policy Guidelines**

According to the joint statement on diagnosis and management of alpha-1 antitrypsin deficiency by
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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 evidence for genetic testing for individuals with suspected AATD and serum AAT level in the range of severe deficiency, includes studies on analytic and clinical validity, and several controlled studies assessing potential clinical utility. Relevant outcomes are test accuracy and validity, symptoms, and morbid events. Knowledge of AATD status may lead to behavior changes or changes in medical management that lead to improved health outcomes; however, there is limited supportive published evidence. The available evidence suggests that knowledge of AATD status may discourage non-smokers from initiating smoking and may increase quit attempts among smokers, but it has not been shown to increase successful quitting.

A Cochrane systematic review of 3 RCTs on AAT augmentation therapy had mixed findings; change in lung density, but not other outcomes, improved with treatment. There is a lack of direct evidence to demonstrate clinical utility. A chain of evidence suggests that making a diagnosis of AATD in individuals with suspected AATD can support clinical utility. 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-studies that individuals who know from birth they have AATD are less likely to initiate smoking than individuals without genetic information knowledge. The evidence is insufficient to determine the effects of technology on health outcomes.

Billing/Coding/Physician Documentation Information

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. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81332

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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Policy Implementation/Update Information

6/29/12 New policy developed. Genetic testing for alpha-1 antitrypsin deficiency may be considered medically necessary when both of the following conditions are met: 1. Patient is
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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; AND 2. Patient has a serum alpha-1 antitrypsin level in the range of
severe deficiency. Medical Director review 5/2012. Policy noticed on 6/29/2012 for
effective date of 10/01/2012. (mco)

2/12/13 Specialty Matched Consultant Advisory Panel review 1/2013. No changes to Policy
Statements. (mco)

5/28/13 References updated. No changes to Policy Statements. (mco)

2/25/14 Specialty Matched Consultant Advisory Panel review 1/2014. Medical Director review
1/2014. No changes to Policy Statements. (mco)

5/27/14 Description section updated. References updated. No changes to Policy Statements. (mco)

Medical Director review 4/2015. Policy Statements remain unchanged. (td)

Medical Director review 3/2016. (jd)

2/24/17 Regulatory status section and Policy Guidelines updated. References updated. Medical
Director review 1/2017 (jd)

3/2017. (jd)

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purposes only and is based on research of current medical literature and review of common medical practices in the treatment
and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review
and revise its medical policies periodically.