Medical Coverage Policy

Genetic Testing for Alpha-1 Antitrypsin (AATD) Deficiency-PREAUTH

☐ Device/Equipment  ☐ Drug  ☐ Medical  ☐ Surgery  ☒ Test  ☐ Other

Effective Date: 7/1/2013  Policy Last Updated: 1/22/2013

☒ Prospective review is recommended/required. Please check the member agreement for preauthorization guidelines.

☐ Prospective review is not required.

Description:
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. 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 addition, individuals with AATD are advised to avoid other substances that 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-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.

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. (3)

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). 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. (5) 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. (6)

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.

**Medical Criteria:**
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 (parent, child or sibling) with AAT deficiency:

   * Clinical factors include the following:
     - 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

   **AND**

2. Patient has a serum alpha-1 antitrypsin level in the range of severe deficiency (See table below).

The following table shows the range of serum levels of alpha-1 antitrypsin by common phenotypes according to the commercial standard milligram per deciliter (mg/dL) and the purified standard micromole (uM). A level of less than 11 uM is generally considered to be associated with an increased risk of clinical disease, but this cut-off may vary according to the specific test used.

<table>
<thead>
<tr>
<th>Phenytype</th>
<th>MM (uM)</th>
<th>MZ (uM)</th>
<th>SS (uM)</th>
<th>SZ (uM)</th>
<th>ZZ (uM)</th>
<th>Znull (uM)</th>
<th>Null-Null (uM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mg/dL</td>
<td>150-350</td>
<td>90-210</td>
<td>100-200</td>
<td>75-120</td>
<td>20-45</td>
<td>&lt;20</td>
<td>0</td>
</tr>
</tbody>
</table>

Genetic testing for alpha-1 antitrypsin deficiency is considered not medically necessary in all other situations.

**Policy:**
Genetic testing for alpha-1 antitrypsin deficiency is considered medically necessary for conditions listed in the medical criteria above for all BCBSRI products.

**Coverage:**
Benefits may vary between groups/contracts. Please refer to the appropriate Evidence of Coverage or Subscriber Agreement for applicable genetic testing coverage/benefits.
Medicare excludes all screening (not just genetic screening) with certain statutory exceptions. BlueCHiP for Medicare provides no additional benefits for genetic screening. Only if the patient exhibits signs or symptoms of the disease would the test not be considered screening.

Coding:
The following CPT code is medically necessary and requires/recommends preauthorization.
81332

Also known as:
Phenotyping test

Related topics:
Genetic Counseling
Genetic Testing

Published:
Provider Update: July 2013

References:
Blue Cross and Blue Shield Association; Medical Policy Reference Manual Policy 2.04.79 Genetic Testing for Alpha-1 Antitrypsin Deficiency

Review History:
01/22/2013: New policy created.

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