Corporate Medical Policy

Genetic Testing for Alpha-1 Antitrypsin Deficiency AHS-M2068

Description of Procedure or Service

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

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

Policy
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

1. Genetic testing for alpha-1 antitrypsin is considered medically necessary when a patient has a serum alpha-1 antitrypsin level in the range of severe deficiency (based on institutional reference range) AND all of the following conditions are met:
   A. Patient is suspected of having alpha-1 antitrypsin deficiency because of the following clinical factors
      1. Early-onset emphysema (age of 45 years or less); OR
      2. Emphysema in the absence of a recognized risk factor (smoking, occupational dust exposure, etc.); OR
      3. Emphysema with prominent basilar hyperlucency; OR
      4. Otherwise unexplained liver disease; OR
      5. Necrotizing panniculitis; OR
      6. Anti-proteinase three-positive vasculitis (C-ANCA [anti-neutrophil cytoplasmic antibody]-positive vasculitis); OR
      7. Bronchiectasis without evident etiology; OR
   8. The patient is considered high risk of having alpha-1 antitrypsin deficiency due to a first-degree relative with AAT deficiency. Note: first-degree relative is defined as a parent, child or sibling
Genetic Testing for Alpha-1 Antitrypsin Deficiency AHS-M2068

B. Patient has discordant results between serum levels and proteotype testing for Z and S alleles by mass spectrometry

2. Isoelectric focusing/phenotyping or gene sequencing is considered medically necessary when there is strong suspicion of the disease based on laboratory testing and symptoms and individual has a negative genotype testing for common variants or proteotype.

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

Background

Alpha-1 Antitrypsin deficiency (AATD) is a result of abnormal alpha-1 antitrypsin (AAT) protein inherited in an autosomal recessive pattern with codominant expression (Hartz, 2012) in which both genes inherited can be active and contribute to the genetic trait they control. AAT is a protease inhibitor (Pi) of the proteolytic enzyme elastase and also of the proteases trypsin, chymotrypsin, and thrombin (Hartz, 2012). Genes with atypical or null alleles produce AAT protein that is either deficient in amount or in function. The AAT protein is produced in the liver and has role in protecting lungs from injury by neutrophil elastase, which is secreted by white blood cells as a response to inflammation or infection (J. K. Stoller & Aboussouan, 2012). If the enzyme remains unchecked by AAT protein, damage to alveoli and resulting chronic obstructive pulmonary disease can occur. This includes emphysema, bronchiectasis, and spontaneous pneumothorax. Smoking and other environmental exposure can make this damage worse (J. Stoller, 2018b).

Abnormal molecules of AAT protein caused by this illness can also cause liver dysfunction. Pathologic polymerization of the variant AAT, resulting in intrahepatocyte accumulation of AAT molecules (J. Stoller, 2018b), leading to cirrhosis, fibrosis, cholestasis, or hepatomegaly. Liver disease is more common in individuals with certain allele combinations. Male gender and obesity may be risk factors for progression to advanced liver disease in adulthood among patients with severe AAT deficiency. In contrast, alcohol use and viral hepatitis do not appear to increase the risk of progressive hepatic failure (Bowlus et al., 2005). It is important to note that AATD is the most common genetic cause of liver disease in children.

Skin manifestations of AATD are also recognized. The most commonly associated skin condition is an illness called necrotizing panniculitis (ATS/ERS, 2003). 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 (Gross et al., 2009). Associations between alpha-1 antitrypsin (AAT) and vascular disease, inflammatory bowel disease, glomerulonephritis, and vasculitis have been proposed but not definitively established (J. Stoller, 2018b).

It is estimated (Campos, Wanner, Zhang, & Sandhaus, 2005) that 80,000 to 100,000 people in the United States have the severe form of the disease (homozygous in null or abnormal alleles). There is much variation in the disease prevalence in other nations (de Serres, Blanco, & Fernandez-Bustillo, 2007). Most current estimates are that 3 million people worldwide have severe AATD.

Testing for AATD starts with suspicion of disease and review of clinical information (medical history, radiographs, pulmonary function tests, and family history). Any individuals with incompletely reversible airflow obstruction after intensive treatment should be considered for initial AATD testing (this is not inclusive of genetic testing). The following should also lead to clinical suspicion of AATD: history of lung or liver disease, emphysema at young age (<45), liver disease (especially pediatric population), necrotizing panniculitis, C-ANCA (cytoplasmic antineutrophil cytoplasmic antibodies) positive vasculitis, certain laboratory abnormalities (elevated liver enzymes,
Genetic Testing for Alpha-1 Antitrypsin Deficiency AHS-M2068

low alpha1-globulin or presence in protein electrophoresis of two alpha 1 globulin bands),
emphysema and non-smoking status, or chest radiograph findings of basilar emphysema (Miravitlles et al., 2017).

Initial testing begins with serum quantification of AAT protein (Miravitlles et al., 2010). This can be done through several methods (immunodiffusion, immune turbidimetry, rocket immunoelectrophoresis, or nephelometry) (J. Stoller, 2018a). A low level is generally represented by a serum level below 11 micromol/L (less than 80 mg/dl using radial Immunodiffusion method or level of less than 50 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 by one of the techniques below (ATS/ERS, 2003).

Isoelectric immunophenotype testing uses the difference in migration rates of allele variants under isoelectric focusing. This is not a genetic test. Interpretation of these results must be done by a capable laboratory. On occasion the results can be inconclusive or discordant with quantitative testing, requiring genotype testing of the most-common variants (J. Stoller, 2018a).

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. It is important that informed consent and counseling be provided to individuals meeting criteria and wishing to pursue this testing (J. Stoller, 2018a).

However more recent evidence from the Alpha-1 Foundation (Sandhaus et al., 2016) suggest “For diagnostic testing of symptomatic individuals, we 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.”

When dealing with the possibility of a rare variant or null allele, full gene sequencing can be utilized as a final diagnostic measure (Stoller, 2017).

Validity and Utility
The literature on the analytic and clinical validity of genetic testing for AATD is limited. In addition, there are few randomized controlled trials (RCTs) evaluating the impact of AATD testing on patient outcomes. There are current evidence-based guidelines (Vogelmeier et al., 2017) for diagnosis and management of AATD that recommend specific interventions for patients with emphysema and AATD. AAT augmentation therapy is often prescribed for patients with AATD and chronic obstructive pulmonary disorder (COPD). In addition, several studies have documented that the disease is under-recognized with delay in diagnosis of between 5 to 8 years (Barrecheeguren et al., 2016; J. K. Stoller et al., 2005).

Applicable Federal Regulations
There are 12 FDA cleared (FDA, 2018a) Alpha-1 antitrypsin immunological test systems approved between 1977 and 2013.

On November 17, 2017 the FDA approved Grifol’s (Grifols, 2017) Serpina1 Variant Detection System as a qualitative in vitro molecular diagnostic system used to detect variants in SERPINA1 gene in genomic DNA isolated from human specimens.

On April 6, 2017 the FDA approved (FDA, 2017) the 23andMe PGS Genetic Health Risk Report for Alpha-1 Antitrypsin Deficiency (AATD) which determines if a person has variants associated with a higher risk of developing AATD associated lung or liver disease. This report is based on a qualitative genetic test for single nucleotide polymorphism detection of the PI*Z (rs28929474) and PI*S (rs17580) variants in the SERPINA1 gene by using the 23andMe Personal Genome Service.
Genetic Testing for Alpha-1 Antitrypsin Deficiency AHS-M2068

**Guidelines and Recommendations**

There are published guidelines and recommendations surrounding genetic testing for AATD. The most notably is the *American Thoracic Society/ European Respiratory Society Statement: Standards for the Diagnosis and Management of Individuals with Alpha-1 Antitrypsin Deficiency*. These recommendations take into account family impact, psychological impact, adverse social effects, age of the individual being tested, economic impact, and potential effects on procreation and health behaviors. The literature strongly supports informed consent and counseling to coincide with genetic testing. These recommendations are outlined in the policy guideline section below.

The American College of Gastroenterology (Kwo, Cohen, & Lim, 2017) also states that initial testing for AATD be done for patients with nonalcoholic fatty liver disease and alcoholic liver disease. They strongly recommend persons with elevated transaminases (AST and ALT) also be screened for AATD. They state that if genetic testing is pursued it should include genetic counseling.

**World Health Organization**

The World Health Organization (WHO, 1997) recommends the testing of all COPD patients.

**European Respiratory Society**

The European Respiratory Society (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 Alpha-1 Foundation**

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

- For 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.
- 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, we 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.

**Policy Guidelines**
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:

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

Type B recommendations for diagnostic testing in the following situations:

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

Type C recommendations for diagnostic testing in the following situations

1. Adults with asthma in whom airflow obstruction is completely reversible
2. Predispositional testing
3. Population screening of smokers with normal spirometry

Type D recommendations for diagnostic testing in the following situations:

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

* Population screening is not recommended currently. However, a possible exception (type B recommendation) may apply in countries satisfying all three of the following conditions: (1) the prevalence of AAT deficiency is high (about 1/1,500, or more); (2) smoking is prevalent; and (3) adequate counseling services are available.

According to the 2003 joint statement on diagnosis and management of alpha-1 antitrypsin deficiency by the American Thoracic Society/European Respiratory Society: (1)
Genetic Testing for Alpha-1 Antitrypsin Deficiency AHS-M2068

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

**Clinical Factors**
1. Early-onset emphysema (age of 45 years or less)
2. Emphysema in the absence of a recognized risk factor (smoking, occupational dust exposure, etc.)
3. Emphysema with prominent basilar hyperlucency
4. Otherwise unexplained liver disease
5. Necrotizing panniculitis
6. Anti-proteinase three-positive vasculitis (C-ANCA [anti-neutrophil cytoplasmic antibody]-positive vasculitis)
7. Bronchiectasis without evident etiology

**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: 82103, 82104, 82542, 81332, 83789*

<table>
<thead>
<tr>
<th>Code Number</th>
<th>PA Required</th>
<th>PA Not Required</th>
<th>Not Covered</th>
</tr>
</thead>
<tbody>
<tr>
<td>82103</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>82104</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>82542</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>81332</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>83789</td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

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**


Genetic Testing for Alpha-1 Antitrypsin Deficiency AHS-M2068


**Policy Implementation/Update Information**

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

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational 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.