Protocol

Genetic Testing for Alpha$_1$-Antitrypsin Deficiency

(20479)

Medical Benefit		**Effective Date**: 01/01/13	**Next Review Date**: 09/17
Preauthorization	Yes	**Review Dates**: 09/12, 09/13, 09/14, 09/15, 09/16	

Preauthorization is required.

The following Protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • With suspected alpha$_1$-antitrypsin deficiency and serum alpha$_1$-antitrypsin level in the range of severe deficiency	Interventions of interest are: • Genetic testing	Comparators of interest are: • Standard care without genetic testing	Relevant outcomes include: • Test accuracy • Test validity • Symptoms • Morbid events

Description

Alpha$_1$-antitrypsin deficiency (AATD) is an autosomal recessive genetic disorder that causes 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. This Protocol addresses the following category of genetic testing: (1) diagnostic testing of an individual's germline to benefit the individual and (2) testing an asymptomatic individual to determine future risk of disease.

Summary of Evidence

The evidence for genetic testing in individuals who have suspected alpha$_1$-antitrypsin deficiency (AATD) and serum alpha$_1$-antitrypsin (AAT) level in the range of severe deficiency includes several studies on analytic and clinical validity, and several controlled studies assessing clinical utility. Relevant outcomes are test accuracy and validity, symptoms, and morbid events. 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 randomized controlled trials on AAT augmentation therapy is 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. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

Policy

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 alpha$_1$-antitrypsin deficiency (see Policy Guidelines); AND
2. Patient has a serum alpha$_1$-antitrypsin level in the range of severe deficiency (see Policy Guidelines).

Genetic testing for alpha$_1$-antitrypsin deficiency is considered **investigational** in all other situations.

Policy Guidelines

According to the 2003 joint statement on diagnosis and management of AATD by the American Thoracic Society/ European Respiratory Society,[1] the following features should prompt suspicion by physicians that their patient may be more likely to have AATD:

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

Family history

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

AATD occurs largely in whites. For example, the prevalence is Sweden is approximately one in 1,575 and the estimated prevalence in the United States is between one in 2,857 and one in 5,097.[1]

The following table shows the range of serum levels of AAT by common phenotypes according to the commercial standard milligram per deciliter (mg/dL) and the purified standard micromole (µmol). A level of less than 11 µmol 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 (American Thoracic Society & European Respiratory Society, 2003; Global Initiative for Chronic Obstructive Lung Disease, 2011):

Range of Alpha1-Antitrypsin Serum Levels by Common Phenotypes

	MM	MZ	SS	SZ	ZZ	Znull	Null-Null
µmol	20-48	17-33	15-33	8-16	2.5-7	< 2.5	0
mg/dL	150-350	90-210	100-200	75-120	20-45	< 20	0

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The inter-pretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic

testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Background

Description of Disease

AATD is an autosomal recessive genetic disorder that decreases 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 one in 2857 and one in 5097 individuals, respectively.[1]

AAT is an acute phase glycoprotein, primarily synthesized 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 and can damage lung tissue if its action is not regulated by AAT. Individuals with AATD thus have an increased risk of lung disease.

Respiratory disease tends to be more severe and occur sooner (i.e., between ages 40 and 50 years) in individuals with AATD who smoke cigarettes and/or are exposed to occupational dust or fumes. In nonsmokers 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. Adults with AATD-associated liver disease generally present with cirrhosis and fibrosis. Panniculitis is a rare, but well-recognized complication of AATD. This dermatologic condition is characterized by inflammatory and necrotizing lesions of the skin and subcutaneous tissue.[2]

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.[1] In addition, individuals with AATD are advised to avoid other substances that can irritate the lungs (e.g., cigarette smoke, dust, workplace chemicals), as well as substances that can cause liver damage (e.g., alcohol). 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 COPD. One treatment option that is specific to AATD is AAT augmentation. There are commercially available intravenous AAT augmentation products; patients generally receive injections of plasma every three to four weeks for life. Inhaled AAT augmentation therapy is under development. There is a lack of consensus about the efficacy of augmentation treatment.

Diagnostic Testing for AAT

Several types of tests are available for patients suspected of having AATD. A blood test is available that quantifies the total amount of AAT 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 AATD. In general, a serum concentration of AAT less than 15% to 20% of the normal value is highly suggestive of a homozygous AAT 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 with 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 codominant (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 two copies of the normal M allele sequence (MM) and have mean serum concentrations of AAT ranging from 20 to 53 µmol/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 µmol/L and a high risk of chronic obstructive pulmonary (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.[4]

Genetic testing for AATD can be done with the alpha$_1$ genotype test. This test uses polymerase chain reaction 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., 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 Mayo Clinic, is to perform serum protein quantification, followed by genotype testing in subjects with clinical suspicion of AATD. If these tests are discordant, phenotype testing is then performed.[6]

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 the qualitative detection and identification of the phenotypes of alpha$_1$-antitrypsin protein. FDA product code: OBZ.

No FDA-cleared genotyping tests were found. Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, FDA has chosen not to require any regulatory review of this test.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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