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Medical Policy Manual

Topic: Genetic Testing for Alpha-1 Antitrypsin Deficiency

Date of Origin: May 2013

Section: Genetic Testing

Last Reviewed Date: May 2014

Policy No: 61

Effective Date: August 1, 2014

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

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. 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] 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.

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. Therefore, individuals with AAT deficiency 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 a well-recognized complication of AAT deficiency. This dermatological 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 individuals who are homozygous for the most severe AAT mutations.[1] In addition, individuals with AATD are advised to avoid other substances that can cause liver damage. There are also general recommendations to exercise, avoid stress and have a nutritious diet. Furthermore, more aggressive treatments for conditions such as asthma outbreaks or acute exacerbations of chronic obstructive pulmonary disease (COPD) may be recommended for patients with AATD. 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; however, there is a lack of consensus about the efficacy of this treatment.[3]

Diagnostic Testing for Alpha-1 Antitrypsin Deficiency (AATD)

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]

Genetic testing is also available for patients suspected of having AATD. 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, characterized by mean serum concentrations of AAT between 2.5 to 7 umol/L and a high risk of COPD. Individuals with rarer mutations of the SERPINA1 gene or null alleles may not produce any AAT and are also at high risk.[5] Individuals with genotype SS and heterozygous individuals with genotype MZ have low risk of COPD and moderately lower levels of 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.[6] 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.[7]

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.). 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 identified. 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 POLICY CRITERIA

Genetic testing for alpha-1 antitrypsin deficiency is considered **investigational** for all indications.

SCIENTIFIC EVIDENCE

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.

Literature Appraisal

Analytic Validity

Analytic performance of the Hydrogel AAT phenotyping test was reported in a U.S. Food and Drug Administration (FDA) decision summary document.[8] 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 AAT genotyping test conducted in the United States, other than FDA documents, were identified.

Clinical Validity

- In 2008, Ljujic and colleagues published findings of a study with 27 emphysema patients.[9] Phenotyping was performed using isoelectric focusing and genotyping by denaturing gradient gel electrophoresis (DGGE). 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.

- The FDA decision summary for the Hydrogel phenotyping test included an evaluation of clinical sensitivity and specificity.[8] Samples were evaluated from 64 patients with the following diagnoses: congenital AATD [alpha-1 antitrypsin deficiency] (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 39/39 (100%) and the specificity was 23/25 (92%). (Note: This analysis excluded 4 individuals with indeterminate diagnoses).

Clinical Utility

The clinical utility of genetic testing for alpha-1 antitrypsin deficiency (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 [alpha-1 antitrypsin protein] status could lead to behavior change that improves health outcomes. In particular, asymptomatic smokers could quit smoking which may prevent or delay onset of lung disease. Whereas, symptomatic smokers could quit smoking which may 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.[10]

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

Smoking Cessation

In 2003, the American Thoracic Society (ATS) and the European Respiratory Society (ERS) published a joint statement on diagnosis and management of alpha-1 antitrypsin deficiency (AATD), based on systematic reviews and an evidence-based approach to evaluating published data.[1] 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, an RCT on a related topic was identified which found that, at one year, individuals 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, although quit rates did not differ significantly in the two groups.[11]

In 2007, Carpenter and colleagues reported on findings of a survey of individuals who had volunteered for genetic testing for AATD.[12] A total of 4,344 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 brochure. Results of the testing

revealed that 2,228 (56%) of the valid samples tested normal, 1,530 (38%) were found to be heterozygous carriers for AATD (MZ genotype) and 255 (6%) were found to be severely alpha-1 antitrypsin (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 non-respondents. Authors reported that 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 (standard deviation [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. In addition, the low response rate made conclusions difficult regarding the behavior of smokers who were identified as having moderate or severe AATD. Overall, evidence is lacking regarding the impact of AAT status on smoking cessation. Large randomized controlled trials comparing cessation rates in patients with and without AAT testing are needed in order to determine whether knowledge of AAT status significantly impacts patient health decisions.

Smoking Prevention

The ATS/ERS joint statement on AATD noted 2 case-control studies that included children identified at birth as having AATD and matched to a demographically similar control group.[13,14] The number of children with AATD was 61 in one 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 to the control individuals.[1] These studies are limited in number and by small sample size which make conclusions regarding the clinical significance of AAT status on smoking prevention uncertain. In addition, neither of these two studies performed long-term follow-up on the AATD affected group past the single survey of smoking attitudes and rates in early adolescents (around 18-20 years of age). Comparative studies between children with and without AATD who have received testing are needed to determine whether anti-smoking attitudes and lower smoking rates are sustained over time.

Treatment for Individuals with AATD

- Alteration of Timing or Intensity of Treatments for Patients with AATD

  The ATS/ERS recommendations for treating AATD patients with pulmonary disease are the same as the recommendations for patients with COPD, in general.[1] No controlled studies specific to AATD were cited in support of these recommendations to determine whether the timing, intensity, or compliance with these treatments is altered by knowledge of AATD status.

- Apha-1 Antitrypsin Augmentation Therapy

  A 2010 Cochrane review addressed the benefits and harms of augmentation therapy with alpha-1 antitrypsin (AAT) in patients with AADT and lung disease.[15] The investigators searched for randomized controlled trials (RCTs) comparing augmentation therapy with AAT to placebo or no

intervention and reporting one or more of the primary outcomes: mortality, forced expiratory volume in one second (FEV1) or adverse effects. Two RCTs were identified; both were conducted by the same research team.[16,17]

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, and 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 to 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 computed tomography (CT) findings favored the treatment group. The mean difference was 1.14, 95% CI: 0.14 to 2.14, p=0.026. The Cochrane review authors noted a potential financial conflict of interest in the first study and a selective reporting of outcomes in the second trial, specifically related to the trial authors' emphasis on the intermediate outcome of CT lung density.

The Cochrane review concluded that there was insufficient evidence to recommend augmentation therapy with alpha-1 antitrypsin.

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.

Conclusion

Limited evidence suggests 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 suggesting that individuals who know from birth they have AATD, are less likely to initiate smoking than individuals without genetic testing information. However, these studies are limited by short-term follow-up which preclude conclusions regarding the long-term impact of AAT testing status on smoking prevention.

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 alpha-1 antitrypsin augmentation therapy is effective for improving health outcomes in individuals with AATD.

Clinical Practice Guidelines

American Thoracic Society (ATS) and the European Respiratory Society (ERS)

In 2003, the ATS and ERS published a joint statement with recommendations on the diagnosis and management of individuals with AAT deficiency.[1] Of note, the ATS and ERS issued these recommendations with grading classifications, and stated that, "each recommendation type was based on the level of supportive evidence for each issue regarding testing." However, the quality of the evidence used to assign grades to these recommendations was not clearly defined within the joint statement.

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

Global Initiative for Chronic Obstructive Lung Disease (GOLD)[18]

The 2013 GOLD guidelines regarding the diagnosis, management, and prevention of chronic obstructive pulmonary disease indicated that young patients with severe hereditary alpha-1 antitrypsin deficiency and established emphysema may be candidates for augmentation therapy; however this recommendation was based upon lower-level evidence from nonrandomized trials. The GOLD guidelines were silent regarding genetic testing for diagnosing or treating AAT deficiency.

Summary

The current evidence has not demonstrated how alpha-1 antitrypsin deficiency (AATD) genetic test results have impacted smoking prevention or cessation. Due to the lack of sufficient evidence demonstrating how testing may improve health decisions or change patient treatment, genetic testing for AATD is considered investigational for all indications.

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CROSS REFERENCES

Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20

CODES	NUMBER	DESCRIPTION
CPT	81332	*SERIPINA 1(serpin peptidase inhibitor, clade A, alpha-1 antiproteinase, antitrypsin, member 1)*(e.g., alpha-1-antitrypsin deficiency), gene analysis, common variants (e.g., *S and *Z)
HCPCS	None	