FEP Medical Policy Manual

FEP 2.04.79 Genetic Testing for Alpha1-Antitrypsin Deficiency

Effective Date: April 15, 2018
Related Policies: None

Genetic Testing for Alpha1-Antitrypsin Deficiency

Description
Alpha1-antitrypsin deficiency (AATD) is an autosomal recessive genetic disorder that results in decreased production of functional alpha1-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. Available tests measure serum AAT levels and phenotype AAT protein variants. Genetic testing is also available to detect the most common pathogenic variants associated with AATD.

FDA 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 through the 510(k) process for the qualitative detection and identification of the phenotypes of AAT protein.

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 Amendments (CLIA). To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

POLICY STATEMENT
Genetic testing for alpha1-antitrypsin deficiency may be considered medically necessary when both of the following conditions are met:

1. Patient is suspected of having alpha1-antitrypsin deficiency because of clinical factors and/or because the patient may be at high risk of having alpha1-antitrypsin deficiency due to a first-degree relative with alpha1-antitrypsin deficiency (see Policy Guidelines section); AND
2. Patient has a serum alpha1-antitrypsin level in the range of severe deficiency (see Policy Guidelines section).

Genetic testing for alpha1-antitrypsin deficiency is considered investigational in all other situations.

POLICY GUIDELINES
According to the 2003 joint statement on diagnosis and management of alpha1-antitrypsin deficiency by the American Thoracic Society and European Respiratory Society, the following features should prompt suspicion by physicians that their patient may be more likely to have alpha1-antitrypsin deficiency.

Clinical factors:
FEP 2.04.79 Genetic Testing for Alpha1-Antitrypsin Deficiency

- Early-onset emphysema (age ≤45 years)
- Emphysema in the absence of a recognized risk factor (eg, smoking, occupational dust exposure)
- Emphysema with prominent basilar hyperlucency
- Otherwise unexplained liver disease
- Necrotizing panniculitis
- Anti-proteinase 3-positive vasculitis (cytoplasmic anti-neutrophil cytoplasmic antibody–positive vasculitis)
- Bronchiectasis without evident etiology.

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

Alpha1-antitrypsin deficiency occurs largely in whites. For example, the prevalence in Sweden is approximately 1 in 1575; the estimated prevalence in the United States is between 1 in 2857 and 1 in 5097 (American Thoracic Society & European Respiratory Society, 2003).

Table PG1 shows the range of serum levels of alpha1-antitrypsin by common phenotypes according to the commercial standard milligram per deciliter and the purified standard micromole. A level less than 11 µmol is generally considered to be associated with an increased risk of clinical disease, but this cutoff may vary by the specific test used (American Thoracic Society & European Respiratory Society, 2003; Global Initiative for Chronic Obstructive Lung Disease, 2016)

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>MM (µmol)</th>
<th>MZ (µmol)</th>
<th>SS (µmol)</th>
<th>SZ (µmol)</th>
<th>ZZ (µmol)</th>
<th>Znull (µmol)</th>
<th>Null-Null (µmol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mmol</td>
<td>20-48</td>
<td>17-33</td>
<td>15-33</td>
<td>8-16</td>
<td>2.5-7</td>
<td>&lt;2.5</td>
<td>0</td>
</tr>
<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>

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG2). The Society's nomenclature is recommended by the Human Variome Project, the HuMan Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG3 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

<table>
<thead>
<tr>
<th>Previous Definition</th>
<th>Updated Definition</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
<td>Change in the DNA sequence</td>
</tr>
<tr>
<td>Variant familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
</tr>
</tbody>
</table>

Table PG3. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
</tbody>
</table>

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.
**FEP 2.04.79 Genetic Testing for Alpha1-Antitrypsin Deficiency**

**Likely pathogenic**
- Likely disease-causing change in the DNA sequence

**Variant of uncertain significance**
- Change in DNA sequence with uncertain effects on disease

**Likely benign**
- Likely benign change in the DNA sequence

**Benign**
- Benign change in the DNA sequence

American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

**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 interpretation 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.

**BENEFIT APPLICATION**

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient’s existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

**RATIONALE**

**Summary of Evidence**

For individuals who have suspected AATD who receive genetic testing for AATD, the evidence includes studies on clinical validity, and several controlled studies assessing potential clinical utility. Relevant outcomes are test accuracy and validity, symptoms, and morbid events. Genetic testing can confirm a diagnosis of AATD suggested by serum testing by identifying the known genetic variants associated with the disease and identify AATD when a diagnosis is uncertain due to the suspicious clinical presentation that is not confirmed by serum testing. A chain of evidence suggests that making a diagnosis of AATD in individuals with suspected AATD can support clinical utility by allowing monitoring for multisystem complications and initiation of accepted therapies. 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 evidence. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**SUPPLEMENTAL INFORMATION**

**Practice Guidelines and Position Statements**

**Canadian Thoracic Society**

In 2012, the Canadian Thoracic Society published clinical practice guidelines on alpha1-antitrypsin deficiency (AATD) testing and alpha1-antitrypsin (AAT) augmentation therapy.20 The recommendations for targeted testing for AATD included:

---

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.
FEP 2.04.79 Genetic Testing for Alpha1-Antitrypsin Deficiency

- Targeted testing for AATD may be considered in those individuals with chronic obstructive pulmonary disease (COPD) who were either diagnosed before 65 years of age or who had less than a 20 pack-year history of smoking.
- Targeted testing for AATD was not recommended in individuals with bronchiectasis or asthma.

American Thoracic Society and European Respiratory Society
In 2003, the American Thoracic Society and European Respiratory Society published joint recommendations on the diagnosis and management of individuals with AATD. Table 1 summarizes the relevant recommendations.

Table 1 Recommendations for Diagnosis and Management of AATD

<table>
<thead>
<tr>
<th>Recommendations for Diagnostic Testing</th>
<th>GOR^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Symptomatic adults with emphysema, chronic obstructive pulmonary disease (COPD), or asthma with airflow obstruction that is not completely reversible with aggressive treatment with bronchodilators....&quot;</td>
<td>A</td>
</tr>
<tr>
<td>&quot;Individuals with unexplained liver disease...&quot;</td>
<td></td>
</tr>
<tr>
<td>&quot;Asymptomatic individuals with persistent obstruction on pulmonary function tests with identifiable risk factors (eg, cigarette smoking, occupational exposure)&quot;</td>
<td></td>
</tr>
<tr>
<td>&quot;Adults with necrotizing panniculitis...&quot;</td>
<td></td>
</tr>
<tr>
<td>&quot;Siblings of an individual with known AAT deficiency&quot;</td>
<td>B</td>
</tr>
<tr>
<td>&quot;Adults with bronchiectasis without evidence etiology&quot;</td>
<td></td>
</tr>
<tr>
<td>&quot;Adolescents with persistent airflow obstruction&quot;</td>
<td></td>
</tr>
<tr>
<td>&quot;Asymptomatic individuals with persistent airflow obstruction and no risk factors&quot;</td>
<td></td>
</tr>
<tr>
<td>&quot;Adults with C-ANCA-positive (anti-proteinase 3-positive) vasculitis&quot;</td>
<td></td>
</tr>
<tr>
<td>&quot;Individuals with a family history of COPD or liver disease not known to be attributed to AAT deficiency&quot;</td>
<td></td>
</tr>
<tr>
<td>&quot;Distant relatives of an individual who is homozygous for AAT deficiency&quot;</td>
<td></td>
</tr>
<tr>
<td>&quot;Offspring or parents of an individual with homozygous AAT deficiency&quot;</td>
<td></td>
</tr>
<tr>
<td>&quot;Siblings, offspring, parents, or distant relatives of an individual who is heterozygous for AAT deficiency&quot;</td>
<td></td>
</tr>
<tr>
<td>&quot;Individuals at high risk of having AAT deficiency-related diseases&quot;</td>
<td></td>
</tr>
<tr>
<td>&quot;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&quot;</td>
<td></td>
</tr>
<tr>
<td>&quot;Adults with asthma in whom airflow obstruction is completely reversible&quot;</td>
<td>C</td>
</tr>
<tr>
<td>&quot;Predispositional testing&quot;</td>
<td></td>
</tr>
<tr>
<td>&quot;Population screening of smokers with normal spirometry&quot;</td>
<td></td>
</tr>
<tr>
<td>&quot;Predispositional fetal testing&quot;</td>
<td>D</td>
</tr>
<tr>
<td>&quot;Population screening of either neonates, adolescents, or adults&quot;^b</td>
<td></td>
</tr>
</tbody>
</table>

AAT: alpha1-antitrypsin; AATD: alpha1-antitrypsin deficiency; C-ANCA: cytoplasmic anti-neutrophil cytoplasmic antibodies; COPD: chronic obstructive pulmonary disease; GOR grade of recommendation.

^a 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 (ie, should not be encouraged); type D: recommend against genetic testing (ie, should be discouraged).

^b 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 1/1500, or more); (2) smoking is prevalent; and (3) adequate counseling services are available.

World Health Organization
A 1997 memorandum published by the World Health Organization following a 1996 meeting on AATD, included the following recommendations relevant to this review21:

- "All patients with COPD and adults and adolescents with asthma [should] be screened once for AAT deficiency using a quantitative test. Those with abnormal results on screening should undergo PI [protease inhibitor] typing.

---

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.
FEP 2.04.79 Genetic Testing for Alpha1-Antitrypsin Deficiency

- “[N]eonatal AAT screening programmes should be undertaken in all developed countries with Caucasian populations.” Among research needs listed is an “Analysis of the costs and benefits of screening, as a prelude to implementing neonatal screening for AAT deficiency.”
- “There is an urgent need for randomized clinical trials of the efficacy of AAT augmentation therapy in persons with the deficiency.”

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

REFERENCES

FEP 2.04.79 Genetic Testing for Alpha1-Antitrypsin Deficiency


**POLICY HISTORY**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>September 2012</td>
<td>New Policy</td>
<td>Policy updated with literature search, no change to policy statement.</td>
</tr>
<tr>
<td>June 2013</td>
<td>Update Policy</td>
<td>Policy updated with literature search, no change to policy statement.</td>
</tr>
<tr>
<td>June 2014</td>
<td>Update Policy</td>
<td>Policy updated with literature review. No references added. No change to policy statements.</td>
</tr>
<tr>
<td>March 2018</td>
<td>Update Policy</td>
<td>Policy updated with literature review through November 6, 2017: reference 3, 4, 8, 9, 14-17, and 19 added. Policy statements unchanged except “not medically necessary” wording corrected to “investigational: due to CLIA testing.”</td>
</tr>
</tbody>
</table>

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.