BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.79 Genetic Testing for Alpha-1 Antitrypsin Deficiency

Effective Policy Date: April 1, 2021

Original Policy Date: September 2012

Related Policies:

None

Genetic Testing for Alpha-1 Antitrypsin Deficiency

Description

Alpha$_1$-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.

OBJECTIVE

The objective of this evidence review is to determine whether genetic testing for alpha1-antitrypsin deficiency in patients with suspected AATD deficiency improves the net health outcomes compared with standard care without genetic testing.

POLICY STATEMENT

Genetic testing for alpha$_1$-antitrypsin deficiency may be considered **medically necessary** when either 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 section); OR
2. Patient has a serum alpha$_1$-antitrypsin level in the range of severe deficiency (see Policy Guidelines section).

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 alpha$_1$-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 alpha$_1$-antitrypsin deficiency.

Clinical factors:

- 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.

Table PG1 shows the range of serum levels of alpha$_1$-antitrypsin by common phenotypes according to the commercial standard milligram per deciliter and the purified standard micromole. A level less than 11 mmol 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 PG1. Range of Alpha1-Antitrypsin Serum Levels by Common Phenotypes

	MM	MZ	SS	SZ	ZZ	Znull	Null-Null
mmol	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

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 PG2. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

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

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
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

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

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.

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

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the FDA has chosen not to require any regulatory review of this test.

RATIONALE

Summary of Evidence

For individuals who have suspected alpha1-antitrypsin deficiency (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; The evidence is sufficient to determine that the technology results in an 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 alpha$_1$-antitrypsin deficiency (AATD) testing and alpha$_1$-antitrypsin (AAT) augmentation therapy.[20,] The recommendations for targeted testing for AATD included:

- 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.[1,] Table 1 summarizes the relevant recommendations.

Table 1. Recommendations for Diagnosis and Management of AATD

Recommendations for Diagnostic Testing	GOR[a]
• "Symptomatic adults with emphysema, chronic obstructive pulmonary disease (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 (eg, cigarette smoking, occupational exposure)" • "Adults with necrotizing panniculitis..." • "Siblings of an individual with known AAT deficiency"	A
• "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"	B
• "Adults with asthma in whom airflow obstruction is completely reversible • "Predispositional testing" • "Population screening of smokers with normal spirometry"	C
• "Predispositional fetal testing" • "Population screening of either neonates, adolescents, or adults"[b]	D

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 3 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.

European Respiratory Society

In 2017, the European Respiratory Society published an updated statement on the diagnosis and treatment of pulmonary disease with AATD.[21,] Statements relating to genetic testing include:

- Quantitative determination of AAT levels is the crucial first step in identifying AATD, which 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, including the rare 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 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 counseling.

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 review[22,]:

- "[A]ll 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."
- "[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. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
September 2012	New policy	
June 2013	Replace policy	Policy updated with literature search, no change to policy statement.
June 2014	Replace Policy	Policy updated with literature review. No references added. No change to policy statements.

Date	Action	Description
June 2015	Replace Policy	Policy updated with literature review. Reference 9 added. Policy statements unchanged.
March 2018	Replace Policy	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.
March 2019	Replace Policy	Policy updated with literature review through November 6, 2017; reference 9 added; reference 4 updated. Policy statements unchanged.
September 2019	Replace Policy	Edits made to Policy Section and Table PG1 Updated; family history language removed from first medically necessary statement due to brochure genetic benefit language
March 2020	Replace Policy	Policy updated with literature review through November 11, 2019; no references added. Policy statements unchanged.
March 2021	Replace policy	Policy updated with literature review through October 19, 2020; no references added. Policy statements unchanged.