**Alpha-1 Antitrypsin Deficiency Testing**

**Introduction**

Alpha-1 antitrypsin deficiency (AATD) testing is addressed by this guideline.

**Procedures addressed**

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan’s procedure code list for management requirements.

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**What is alpha-1 antitrypsin deficiency**

**Definition**

Alpha-1 antitrypsin deficiency (AATD) results from mutations in the SERPINA1 gene, which codes for the enzyme alpha-1 antitrypsin (AAT).¹ This condition is also referred to as AAT Deficiency and A1AT Deficiency.

**Prevalence**

It is estimated that 1 in 5000 to 1 in 7000 people in North America have AATD. AATD commonly afflicts individuals of Northern European heritage. This disorder is most common in Scandinavia, occurring in approximately 1 in 1500 to 1 in 3000 individuals there.¹ However, AATD is an under-recognized condition, with estimates that only 10% of those affected are actually diagnosed.²

**Symptoms**

The most common clinical manifestation is chronic obstructive pulmonary disease (COPD), particularly emphysema.¹⁻³ Smoking is a major environmental risk factor for lung disease in AATD, increasing the risk for emphysema by 1000-fold.³

AATD also increases the risk for neonatal or childhood liver disease, manifested by obstructive jaundice and hyperbilirubinemia, and early onset adult liver disease, usually cirrhosis and fibrosis.¹
Inheritance

Alpha-1 antitrypsin deficiency (AATD) is inherited in an autosomal recessive manner.¹

Diagnosis

AATD may first be suspected based on reduced serum levels of alpha-1 antitrypsin. Confirmatory testing includes either protease inhibitor typing or genetic testing for common mutations.¹

Test information

Introduction

Testing for alpha-1 antitrypsin deficiency may include protease inhibitor typing, SERPINA1 targeted mutation analysis, or SERPINA1 sequencing.

Protease Inhibitor typing

Protease Inhibitor (PI) typing by isoelectric focusing to determine phenotype (PI*Z, PI*S).¹ PI typing is considered the gold standard for diagnosing AATD, as it can detect normal as well as variant alleles, but cannot detect null alleles.¹ Mutation testing should be performed “when serum AAT levels are not measured, PI typing is not performed, or results from serum AAT levels or PI typing are discordant”.¹

SERPINA1 targeted mutation analysis

SERPINA1 targeted mutation analysis tests for the two common mutations in the gene (Z and S), which make up greater than 95% of the mutations.¹ The Z allele is by far the most common and more severe variant.³

SERPINA1 sequencing

SERPINA1 sequencing is available, but only appropriate in limited situations. The proportion of individuals with AATD that have a mutation identified by sequencing is unknown.¹

Guidelines and evidence

Introduction

This section includes relevant guidelines and evidence pertaining to alpha-1 antitrypsin deficiency testing.
American Thoracic Society and the European Respiratory Society recommendations

The American Thoracic Society and the European Respiratory Society states that testing for AATD is recommended for the following indications (quoted directly):³

- symptomatic adults with emphysema, chronic obstructive pulmonary disease (COPD), or asthma with airflow obstruction that is incompletely reversible after aggressive treatment with bronchodilators
- individuals with unexplained liver disease, including neonates, children, and adults, particularly the elderly
- asymptomatic individuals with persistent obstruction on pulmonary function tests with identifiable risk factors, examples include cigarette smoking and occupational exposure
- adults with necrotizing panniculitis, and
- siblings of an individual with AATD.

Other recommendations

The following sections outline recommendations from other authorities. However, these sources do not specifically comment on the use of SERPINA1 sequencing in the diagnostic work-up. When ambiguous results are obtained between quantification, genotype or phenotype assays, gene sequencing can identify rare variants or null alleles that would otherwise be missed.

Sandhaus et al. (2016)⁴

Sandhaus et al. (2016) provided recommendations for the diagnosis of AATD based on systematic review and expert scientist and clinician appraisal. For diagnostic testing of symptomatic individuals, the authors 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”. The authors also recommend that the following groups be tested for AATD.

- “All individuals with COPD, regardless of age or ethnicity”
- “All individuals with unexplained chronic liver disease”
- “All individuals with necrotizing panniculitis, granulomatosis with polyangiitis (GPA, formerly Wegener’s granulomatosis), or unexplained bronchiectasis”

In addition the authors recommend that “adult siblings of individuals identified with an abnormal gene for AAT, whether heterozygote or homozygote, should be provided with genetic counseling and offered testing for AATD”.
Graham et al. (2015)\textsuperscript{5}

Graham et al. (2015) found pathogenic variants with sequencing after PI and targeted mutation analysis were performed. They support full gene sequencing when there is discrepancies between clinical presentation and genotyping after PI and targeted mutation analysis.

Prins et al. (2008)\textsuperscript{6}

Prins et al. (2008) sequenced exons 2, 3, and 5 of the SERPINA1 gene from 66 patients with AAT concentration less than or equal to 1.0 g/L. They predicted that up to 22\% of the disease-associated AAT deficiency alleles could be missed by S and Z genotyping or by phenotyping. They also identified rare alleles $M_{\text{procida}}$, $M_{\text{palermo}}$, $M_{\text{passau}}$, $M_{\text{wurzburg}}$, $M_{\text{heerlen}}$ and the previously undescribed null alleles $Q0_{\text{Soest}}$ and $Q0_{\text{amersfoort}}$.

They found pathogenic variants in 22\% of those who had negative PI and targeted mutation testing. The authors recommend direct sequencing of the coding regions of the SERPINA1 gene for patients with suspected AATD based on a serum AAT concentration ≤1.0 g/L.

Ferrarotti et al. (2007)\textsuperscript{7}

Ferrarotti et al. (2007) described a protocol they developed to optimize AAT deficiency diagnosis from dried blood spot samples. The protocol has an initial screen using quantification of AAT and genotyping for the S and Z deficiency alleles. Discordant samples are then reflexed to PI typing.

Sequencing is used for any samples in which the plasma AAT level is low (<70 mg/dL), and the genotype/phenotype results are PI*MS or PI*MZ. Specific testing for the $Q0_{\text{Isola di procida}}$ allele is also performed, which results from a deletion and therefore cannot be detected by sequencing. While this report described the protocol used, it did not comment on the sensitivity or specificity of this approach.

Criteria

Introduction

Requests for alpha-1 antitrypsin deficiency (AATD) testing are reviewed using these criteria.

Criteria

Protease inhibitor (PI) typing or SERPINA1 common mutation analysis (S, Z) may be considered in individuals who meet the following criteria:\textsuperscript{1,3}

- Abnormally low (less than 120mg/dL) or borderline (90-140mg/dL) alpha-1 antitrypsin (AAT) levels; AND
• At least one of the following:
  o Symptomatic adults with emphysema, chronic obstructive pulmonary disease (COPD), or asthma with airflow obstruction that is incompletely reversible after aggressive treatment with bronchodilators; or
  o Individuals of any age with unexplained liver disease (including obstructive liver disease in infancy); or
  o Asymptomatic individuals with persistent obstruction on pulmonary function tests who have identifiable risk factors (e.g., cigarette smoking, occupational exposure); or
  o C-ANCA positive vasculitis; or
  o Adults with necrotizing panniculitis; or
  o Siblings of an individual with AATD

Sequencing of the SERPINA1 gene may be considered in individuals who meet the following criteria:\(^1\)

• There are discrepancies between clinical presentation, serum alpha-1 antitrypsin quantification, targeted mutation analysis, and/or PI typing; OR
• The presence of rare variants or null alleles (which cannot be identified by other methods) is suspected.

References

Introduction

These references are cited in this guideline.


