Alpha-1 Antitrypsin Deficiency Testing

MOL.TS.124.A
v1.0.2025

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.

Procedures addressed by this guideline	Procedure codes
Protease inhibitor (PI) typing	82104
SERPINA1 sequencing	81479
SERPINA1 targeted mutation analysis	81332

Criteria

Introduction

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

Protease Inhibitor Typing or SERPINA1 Targeted Mutation Analysis

Protease inhibitor (PI) typing or SERPINA1 targeted mutation analysis (*S, *Z) is considered medically necessary in individuals who meet the following criteria:

- Abnormally low (less than 120mg/dL) or borderline (90-140mg/dL) alpha-1 antitrypsin (AAT) levels; AND
- At least one of the following:
  - Symptomatic adults with emphysema, chronic obstructive pulmonary disease (COPD), or asthma with airflow obstruction that is incompletely reversible after aggressive treatment with bronchodilators; or
  - Individuals of any age with unexplained liver disease (including obstructive liver disease in infancy); or

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- Asymptomatic individuals with persistent obstruction on pulmonary function tests who have identifiable risk factors (e.g., cigarette smoking, occupational exposure); or
- C-ANCA positive vasculitis; or
- Adults with necrotizing panniculitis; or
- Siblings of an individual with AATD, AND

- Rendering laboratory is a qualified provider of service per the Health Plan policy.

SERPINA1 Sequence Analysis

Sequencing of the SERPINA1 gene is considered medically necessary in individuals who meet the following criteria:

- 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, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

What is alpha-1 antitrypsin deficiency?

Definition

Alpha-1 antitrypsin deficiency (AATD) is an inherited condition which can affect the lungs, liver, and rarely, skin. 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 affects 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 COPD, particularly emphysema.[1-3] The age of onset for COPD is generally older than 30 years.[1] Lung disease in children with AATD is rare.[1] Smoking is a major environmental risk factor for lung disease in AATD.[1,3]

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] The prevalence of liver disease increases with age.[1] The lifetime

risk of hepatocellular carcinoma (HCC) may also be increased.[1] In more rare cases, individuals with AATD are also at increased risk for panniculitis (tender skin nodules which may be inflammatory and may ulcerate) and C-ANCA positive vasculitis.[1]

Genotype-phenotype correlations for AATD exist (i.e., certain types of mutations in the SERPINA1 gene are expected to be associated with a more severe presentation).[1]

Cause

AATD results from mutations in the SERPINA1 gene, which codes for the enzyme alpha-1 antitrypsin (AAT).[1]

Inheritance

AATD is inherited in an autosomal codominant pattern.[1] Codominance means that two different versions (alleles) of the gene may be active, with both versions contributing to the expression of features. The most common version of the SERPINA1 gene, called PI*M, produces normal levels of AAT.[1] Most people in the general population will have two copies of the PI*M allele (MM).[1] Other alleles of the SERPINA1 gene are anticipated to lead to reduced levels of the AAT enzyme.

For example, the PI*Z allele is the most common pathogenic (disease-causing) allele producing very small amounts of AAT.[1] Individuals who are homozygous (or have two copies) of the PI*Z allele tend to have severe features of AATD.[1] The PI*S pathogenic allele of SERPINA1 produces moderately low levels of AAT.[1] The PI*I allele of SERPINA1 is associated with mildly reduced levels of AAT.[1]

Additional alleles include the PI*F allele ("a pathogenic allele that is distinctive because the resulting protein is functionally impaired in binding neutrophil elastase but quantitatively normal") as well as null alleles ("sometimes designated as PI*QO").[1] PI*QO alleles are "pathogenic alleles that result in either no mRNA product or no protein production."[1]

Disease risks will depend on the combination of SERPINA1 alleles from biological parents. For example, if both biological parents are heterozygous (carriers) for one SERPINA1 PI*Z pathogenic variant, but also have a copy of the normal PI*M allele (denoted MZ), there will be a 25% risk that their offspring are homozygous PI*Z (ZZ).

Diagnosis

AATD may first be suspected based on reduced serum concentration levels of AAT.[1] Confirmatory testing includes either protease inhibitor typing or genetic testing for common mutations.[1] Targeted analysis for the PI*Z, PI*S, PI*I, and PI*F alleles may be performed first.[1] Sequence analysis may be indicated in certain situations.[1]

Management

Individuals with COPD are treated with standard therapy.[1] Individuals with emphysema may be treated with periodic human serum AAT by intravenous infusion.[1] For

individuals with end-stage lung disease, lung transplantation may be considered. "Liver transplantation is the definitive treatment for those with severe disease" as it will restore AAT levels.[1] “Dapsone or doxycycline therapy is used for panniculitis; if refractory to this, high-dose intravenous AAT augmentation therapy is indicated.”[1] Individuals are strongly encouraged to avoid exposure to active and passive smoking, environmental pollutants, and excessive alcohol use.[1] Surveillance includes periodic pulmonary and liver function tests.[1]

Survival

The prognosis for individuals with AATD is dependent on the severity of the disease and lifestyle factors. Individuals with AATD may have a normal lifespan; however, those with exposure to cigarette smoke may experience earlier and faster progression of lung disease.[1]

Test information

Introduction

Testing for AATD may include protease inhibitor typing, targeted mutation analysis, and/or next generation sequencing.

Protease Inhibitor Typing

Protease Inhibitor (PI) typing is performed with isoelectric focusing of serum to determine phenotype.[1] PI typing can detect normal as well as variant alleles, but cannot detect null alleles[1,2]

Targeted Mutation Analysis

Targeted mutation analysis uses hybridization, single nucleotide extension, select exon sequencing, or similar methodologies to assess a set of disease-causing mutations. This analysis identifies common and/or recurring mutations. Targeted mutation panels or select exon sequencing may have differing clinical sensitivities dependent upon ethnicity, phenotypic presentation, or other case-specific characteristics.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Guidelines and evidence

American Thoracic Society and European Respiratory Society

The American Thoracic Society and the European Respiratory Society stated that testing for AATD is recommended for the following indications:[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, (e.g., cigarette smoking, occupational exposure)
- adults with necrotizing panniculitis", and
- "siblings of an individual with AATD."

Selected Relevant Publications

Multiple publications outlined recommendations for the diagnosis of AATD.[4-7]

One study provided recommendations for the diagnosis of AATD based on systematic review and expert scientist and clinician appraisal.[6] They recommended testing for:

- "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 recommended 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”.

For diagnostic testing of symptomatic individuals, the authors recommended “genotyping for at least the S and Z alleles. Advanced or confirmatory testing should include Pi-typing, AAT level testing, and/or expanded genotyping.”

Pathogenic mutations have been detected after negative PI and/or targeted mutation testing.[4,5] One study detected pathogenic mutations in 22% of individuals with negative PI and targeted mutation analysis and recommended direct sequencing of the coding regions of the SERPINA1 gene with suspected AATD due to a serum AAT concentration of ≤1.0 g/L.[4] 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.[4,5]

Another study recommended inclusion of C-reactive protein levels, a marker of inflammation reported to impact observed AAT levels, to decrease the rate of false

negative results in individuals with intermediate deficiency.[7] They found the highest sensitivity by using an approach that evaluated all individuals for AAT levels, serum CRP levels, and genotyping of the S and Z alleles.[7]

Note This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for Alpha-1 Antitrypsin Deficiency testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

References

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