Alpha 1-Antitrypsin: serum levels, phenotyping and genotyping	
Description	Alpha 1-antitrypsin (AAT) is responsible for approximately 90% of the trypsin inhibitory capacity of serum. It is a member of the serine protease inhibitor or serpin superfamily and is also known as alpha 1-protease inhibitor because of its ability to inhibit a broad range of protease enzymes, including trypsin, chymotrypsin, pancreatic elastase, neutral proteases of polymorphonuclear leukocytes and macrophages, and a number of other enzymes. It is a globular glycoprotein that is found in the alpha-1 region of an agarose electrophoresis pattern at pH 8.6. It has a molecular mass of 52 kDa and consists of a 418 amino acid single polypeptide chain with four carbohydrate side chains. AAT is found in serum and in a number of body fluids such as saliva, tears, lymph, semen, cervical mucus, synovial fluid, and human milk. The half-life of exogenous AAT in serum is approximately 1 week, with catabolism taking place in the liver. AAT deficiency is inherited as an autosomal co-dominant disorder, with more than 100 alleles identified. Different phenotypes are classified by a coding system in which the inherited alleles are usually letters that denote the migration of the molecule in an isoelectric pH gradient from A (for anodal variants) to Z (for slower migrating variants). The MM phenotype indicates individuals who are homozygous for the normal allele, and ZZ indicates that they are homozygous for the Z allele. The Z variant consists of a glutamine substitution for a lysine residue at codon 342, causing an AAT-deficient state and a dysfunctional protein. The S variant is due to a substitution of valine for glutamine at codon 264, causing intracellular degradation of the protein. Low serum concentrations of AAT must be confirmed by Pi (protease inhibitor) **phenotyping**. The gold standard for the identification of AAT variants is the phenotyping of serum samples by isoelectric focusing on thin-layer gels in a pH gradient. This can be done on polyacrylamide or agarose gels. The confirmation of Pi*Z and Pi*S can be achieved by **genotyping** using PCR technology and DNA extracted from EDTA blood or from buccal washings. Whilst it is recommended that phenotyping by isoelectric focusing will remain the first line investigation of Pi genetic status, the genotype by DNA analysis is required for admission of an individual to the national AAT deficiency register.
Indication	The quantitation of AAT is indicated in the evaluation of COPD, emphysema and in neonatal and adult liver disease, where low levels may have diagnostic importance. AAT Pi phenotyping should be performed in all cases of deficiency when the quantitative assay gives results below the age-related median concentration. Pi phenotype should be determined in all children with liver disease irrespective of their AAT concentration. Any partners of heterozygotes identified through family screening should also be offered Pi phenotyping so that the 1:20 risk of heterozygous parenthood, which carries a 1:4 risk of an affected child, can be anticipated and appropriate counselling offered.
Additional Info	N/A
Concurrent Tests	Phenotyping and cascade genotyping if necessary.
Dietary Requirements	N/A

Interpretation	The AAT reference interval is 1.1 to 2.3 g/L for subjects with the MM genotype. Age related differences in reference interval have been reported. Following birth, concentrations fall during the first 6 months but rise to adult concentrations by 1 year of age. A number of factors have been reported to increase AAT concentration, including inflammatory disorders, malignancy, trauma, increases in oestrogen concentrations with puberty, pregnancy, or the use of the oral contraceptive pill. However, values rarely increase more than fourfold. These factors can cause considerable overlap in measured concentration between mildly and moderately AAT-deficient subjects and concentrations in normal subjects. Pi M is the commonest phenotype in all populations and racial groups studied. The Pi*S and Pi*Z are more common in the Caucasian than non-Caucasian population. The deficiency alleles include S, P, W, Z, Mmalton, Mduarte and null. The null allele is the allele of complete deficiency and can only be identified by family studies. The reporting of a single allele product (Pi*M) implies the homozygous state, reporting of two alleles (Pi MS) indicates a heterozygote. Frequency of Pi phenotypes in UK Caucasian population: MM=84.2%, MS= 9.8%, MZ=3.6%, FM=0.9%, SZ=0.2% and ZZ=0.04% The risk of emphysema is greatly increased in a person with a severe AAT deficiency if they smoke cigarettes.
Collection Conditions	Serum samples are preferred for AAT concentration determination. Samples may be stored at 4°C for up to 7 days prior to testing. For long-term storage or for samples suspected of a severe deficiency of AAT, storage at −70°C is recommended. Bacterial contamination or improper storage results in altered migration rates of the bands with eventual loss of banding.
Frequency of testing	N/A