1. Introduction

The abundant serum protein alpha-1 antitrypsin (AAT) is the prototype chronic obstructive pulmonary disease (COPD) biomarker. AAT is an antiprotease which inhibits neutrophil-derived proteases and protects the fragile tissues of the lung. Absence of this key antiprotease renders the lung susceptible to proteolytic degradation. Alpha-1 antitrypsin deficiency (AATD) is a hereditary disorder characterised by low circulating levels of alpha-1 antitrypsin (AAT). The lung disease associated with the condition is characterized by neutrophil-dominated airway inflammation and elevated intra-pulmonary protease levels [1]. The SERPINA1 gene encodes for the AAT protein and the most common SERPINA1 mutation known to cause AATD is the Z mutation. The classic case of AATD is an individual homozygous for the Z mutation which causes a severe deficiency of circulating AAT. Intuitively, severe AATD is a proven genetic risk factor for the development of lung and less frequently, liver disease. The condition was previously estimated to play a causative role in approximately 1-2% of COPD cases [2]. However, when intermediate deficiency is included in any evaluation of the contribution of AATD to lung disease, we anticipate that this figure can rise to as high as 10%. Guidelines published by the World Health Organisation (WHO), the American Thoracic Society (ATS), and the European Respiratory Society (ERS) advocate a targeted screening approach for the detection of AATD. Together these organisations recommend testing for AATD in all individuals with COPD regardless of age or smoking history [3, 4]. Despite the clear and significant benefits of correct identification, AATD remains an under-diagnosed
condition with the majority of cases undetected or misdiagnosed as COPD. Less than 10% of ZZ individuals have been correctly identified in Ireland and the same is true in many other countries [5]. In addition, long delays between the presentation of first symptoms and correct diagnosis are commonplace [6]. A diagnosis of AATD can present the doctor and the affected individual with a unique opportunity for early medical intervention and the prevention or postponement of COPD. This is an opportunity that, if seized, has enormous benefits for the affected individual and extended family relatives. This chapter aims to provide healthcare professionals with an overview of AATD and with clinically relevant information to assist them in the recognition, diagnosis, and management of this rarely diagnosed hereditary condition. It is our hope that this information can help counteract the nihilism related to AATD and the reluctance to test that can sometimes exist.

2. What is alpha-1 antitrypsin?

2.1. Clinical manifestations & presentation of AATD

To understand the deficiency, one must first understand the protein. Alpha-1 antitrypsin (AAT) is a 52 kDa glycosylated plasma protein. It belongs to a group of serine protease inhibitors and is encoded by the SERPINA1 gene on chromosome 14q32.1-32.3 [7]. Production of circulating AAT is predominantly the liver and the normal plasma concentration of AAT is 1.5 g/L (1.0-2.0 g/L) with a half-life of 4–5 days [8]. Production of AAT protein has also been shown in other cells such as monocytes, macrophages, pulmonary alveolar cells and intestinal epithelial cells [9-12], hinting at an important role in the local response to tissue inflammation.

AAT is an acute phase protein and plasma levels can rise two to five fold in response to cytokine release (e.g. TNF-α, IL-1 and IL-6) during infection or inflammation [13, 14] with local concentrations at sites of inflammation reaching even higher levels [15].

The association of an absent alpha-globulin band on serum plasma electrophoresis with a possible hereditary form of pulmonary emphysema was first reported by Laurell and Eriksson in 1963 [16]. The observation that these individuals were susceptible to a severe form of hereditary emphysema led to a major breakthrough in our understanding of the role of protease-antiprotease imbalance in the pathogenesis of COPD [17]. Subsequently it was also discovered that people with AATD were also at risk of liver cirrhosis [18]. In the absence of familial or population screening for AATD the majority of people present with clinical symptoms, often at a stage where significant morbidity from the condition has already developed.

2.2. Pulmonary manifestations

Adults with AATD are susceptible to the premature development of lung diseases such as emphysema, chronic bronchitis, bronchiectasis, and asthma. Patients with AATD usually present with exertional breathlessness, wheeze, cough, and frequent pulmonary exacerbations often, but not exclusively with a background history of smoking [19]. Symptoms usually begin from the age of 30 and the clinical suspicion for underlying asthma or chronic obstructive
pulmonary disease (COPD) prompts referral for spirometric assessment. The finding of reversibility on spirometry is common (approximately 50%) and often belies concomitant asthma and emphysema. Reversibility can be associated with a worse prognosis, possibly due to ongoing airway inflammation [19, 20]. The diagnosis of fixed airway obstruction in AATD, indicative of COPD, is often made at a much younger age (<40 years) than the general population. However, screening for AATD is recommended for all adults with COPD or incompletely reversible asthma [4]. Analysis of the Danish AATD registry data of index and non-index cases indicates that the median life expectancy in ZZ homozygotes is reduced dramatically from 69 years to 49 years in smokers compared to non-smokers, and baseline forced expiratory volume in 1 second (FEV1) was the single most important predictor of survival [21, 22]. Cigarette smoke exposure in AATD results in severe impairment of lung function and an accelerated decline in lung function, and affected individuals should be counselled to stop smoking immediately. Occupational exposure to chemicals and pollutants is also independently associated with a decline in lung function in AATD and patients should be advised of using personal protective respiratory equipment where necessary [23, 24].

Figure 1. HRCT findings in ZZ individuals with emphysema (left) and bronchiectasis (right).

The classic pathological finding of bibasal panacinar emphysema can be now readily visualised with the widespread availability of high resolution computed tomography (HRCT) imaging, and the unexpected detection of these changes should prompt the clinician to screen for AATD. CT imaging with lung densitometry measurement facilitates monitoring of disease progression in AATD [25] and may be a superior outcome measure to change in FEV1 in clinical trials examining the effect of augmentation therapy in AATD [26]. CT imaging also permits the identification of bronchiectasis, which may or may not be clinically significant. The reported prevalence of bronchiectasis varies considerably but may occur independently of emphysema and can be severe [27, 28]. Symptoms of bronchiectasis are often difficult to distinguish from COPD and the prevalence and impact of this airway disease in AATD may be underestimated.
2.3. Liver manifestations

A small proportion of ZZ homozygotes present with a neonatal hepatitis syndrome, usually within the first 3-4 months of life. AATD is one of the commonest causes for neonatal hepatitis and can account for up to 29% of cases in some paediatric centres [29]. A large infant screening study of 200,000 newborns identified 120 with the ZZ phenotype, 22 (18.3%) had evidence of a hepatic abnormality. Of this cohort, 14 (11.7%) had prolonged obstructive jaundice and 9 (7.5%) had severe clinical liver disease [30]. The SZ phenotype is also associated with biochemical liver abnormalities, and can lead to end-stage liver disease requiring transplantation, although this is observed less frequently than in ZZ cohorts [31]. A number of risk factors for AATD associated liver disease in childhood have been identified including male gender, renal or pulmonary complications [29], and a first degree relative with AATD-related liver disease [32]. The reported outcomes of childhood liver disease are variable, with one study reporting mortality of 20/74 (27%) and persistent cirrhosis in a similar number [32], although most studies report complete clinical and biochemical recovery of liver function in the majority of cases [29].

Data from the Irish National AATD Registry allowed an investigation of the prevalence of liver abnormalities in a cohort of 115 ZZ individuals (Table 1). A total of 36% had liver function test (LFT) abnormalities on the first assessment, most commonly alanine aminotransferase (ALT), and this did not correlate with increasing age. A further 24% (30/115) were found to have abnormal liver findings by radiology. Fatty infiltration was the most common radiological finding (17%) after examination of abdominal ultrasound results, followed by cirrhosis, liver cysts, and haemangioma. No differences in body mass index (BMI) or alcohol consumption were observed in those with or without liver abnormalities which suggests the frequency of fatty liver was not due to increased obesity or alcohol but more likely to be attributable to the accumulation of Z AAT protein in the liver.

<table>
<thead>
<tr>
<th>Total ZZ</th>
<th>Abnormal Ultrasound</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>115</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>62/53</td>
</tr>
<tr>
<td>Age, years (mean +/- SD)</td>
<td>52 +/- 12</td>
</tr>
<tr>
<td>Mean FEV1 (% predicted)</td>
<td>65 +/- 33</td>
</tr>
<tr>
<td>Mean BMI</td>
<td>26.5</td>
</tr>
<tr>
<td>Alcohol (total respondents)</td>
<td>80</td>
</tr>
<tr>
<td>Active</td>
<td>61</td>
</tr>
<tr>
<td>Past</td>
<td>4</td>
</tr>
<tr>
<td>Never</td>
<td>15</td>
</tr>
</tbody>
</table>

Table 1. Liver abnormality findings in ZZ cohort on Irish National AATD Registry.
In adulthood, a strong relation between AATD and cirrhosis has been reported (OR=7.8; CI 2.4 to 24.7) and primary liver cancer (OR=20; CI 3.5 to 114.3), particularly affecting men [33]. Cirrhosis is usually complicated by portal hypertension, ascites, gastrointestinal bleeding, spontaneous bacterial peritonitis, hepatic encephalopathy, and hepatocellular carcinoma. The prevalence of liver cirrhosis increases with age and usually occurs in those who have never smoked, perhaps as a consequence of the prolonged survival in this group [4, 34]. Both genetic and environmental modifiers play a role in the pathogenesis of liver disease in AATD. Reports of putative candidate modifier genes for AATD-related liver disease have emerged [35-37], however, no specific gene or polymorphism has been conclusively demonstrated to have clinical utility and prognostic value. In addition, the high prevalence of MZ phenotypes in liver disease cohorts and the role of heterozygous AATD in worsening liver disease has been highlighted by several studies [38-40]. Thankfully, the natural history of those with fulminant AATD related liver disease has been dramatically altered by liver transplantation [41] and excellent survival rates have been achieved in adult and paediatric transplant recipients [31, 42].

2.4. Extra-pulmonary manifestations

The rare occurrence of recurrent panniculitis has been noted in individuals with AATD and is thought to relate to persistent neutrophilic inflammation at the affected sites [43]. A number of case reports have reported the panniculitis to be responsive to intravenous augmentation therapy [44-46]. AATD has been associated with a variety of other medical conditions, the best described being ANCA-associated vasculitis and in particular granulomatosis with polyangiitis (GPA). A recent genome wide association study identified the Z allele of SERPINA1 to be associated with Proteinase 3 (PR3)-ANCA positivity [47]. PR3 is inhibited by AAT and some case reports of PR3-ANCA vasculitis in ZZ homozygotes report a severe disease phenotype [48, 49]. The role of AAT in diseases of the circulatory system is incompletely understood. Oxidised AAT can bind to the Apolipoprotein B100 component of LDL in the circulation and may contribute to atherogenesis [50], additionally the cleaved C36 peptide fragment of AAT has been found complexed within atherosclerotic plaques indicating a role in monocyte recruitment within the intima of arterial walls [51]. AAT complexes with IgA were found in the joints and sera of patients with rheumatoid arthritis [52, 53] though there appears to be no strong link between the two conditions [54]. A recent development is the association of diabetes mellitus with low AAT levels [55] and the emerging scientific data demonstrating improved islet cell graft survival in mice transfected with human AAT [56]. However, it is too soon to determine if any sustained benefit can be achieved. Clinical trials are planned to investigate the efficacy of AAT augmentation therapy in diabetes (NCT01183455, NCT02093221).

2.5. AATD heterozygosity: A risk factor for COPD?

An accurate determination of the risk of COPD in AATD heterozygotes is vitally important given the large number of individuals who are potentially affected. We know MZ individuals have moderately reduced levels of AAT but clarifying the risk of COPD in this group has been controversial. The Irish National AATD Targeted Detection Programme has identified over
1,600 MZ individuals in the 12,000 individuals tested to date. While this heterozygote group does include cases identified through family screening, this means that approximately 1 in 8 individuals tested are MZ. Anecdotally, a significant number of MZ individuals from our AATD clinic, both smokers and non-smokers, develop COPD at a relatively young age. Approximately 250,000 individuals on the island of Ireland [5] and 6 million individuals in the United States possess the MZ genotype [57]. A deeper appreciation of the risk of COPD in heterozygotes could lead to the prevention or postponement of lung disease in this group, lessening the growing global healthcare burden of COPD.

During the past 40 years, over 100 studies have attempted to assess the risk of lung disease in MZ individuals. A meta-analysis by Hersh et al estimated that the combined odds ratio for COPD in MZ compared to MM individuals was 2.31. This risk was attenuated in studies which adjusted for cigarette smoke exposure [58]. An accurate determination of the risk of COPD has been fraught with difficulty. Many previous attempts to ascertain the contribution of MZ heterozygosity to the development of COPD have been met with various methodological and design flaws; most notably selection bias and inadequate control for cigarette smoke exposure. A recent study which aimed to clarify the risk of COPD in MZ heterozygotes has addressed many of the concerns which hampered an accurate risk estimate from previous attempts to answer this vitally important question. The issue of selection bias was addressed in the study design by using a family based approach. Index cases or probands were MZ individuals who had a confirmed diagnosis of COPD based on the following spirometric criteria: a post-bronchodilator FEV1/FVC ratio < 0.7 and an FEV1 (% predicted) < 80%. All first degree family members of the index case (proband) underwent AAT phenotyping, pre-and post-bronchodilator spirometry as well as completing the ATS-DLD Epidemiology Questionnaire. For the final analysis, the probands were excluded and the risk of COPD in the MM and MZ first degree relatives was determined. While the main strength of this study was elimination of ascertainment bias, additional strengths included the use of a genetically homogenous population, a standardised criterion for the diagnosis of COPD and adequate control for covariates including age, sex and cigarette smoke exposure. The adjusted odds ratio (OR) for COPD in MZ compared with MM group was 5.18 and this was higher (OR, 10.65) in ever-smoking individuals [59].

A significant gene-by-environment interaction exists to influence the development of COPD in MZ individuals. MZ individuals who have a low exposure to cigarette smoke (< 20 pack-years) have more airflow obstruction compared to MM individuals [59] in addition to more emphysema on quantitative analysis of chest CT scans [60]. This indicates that MZ heterozygosity and cigarette smoke exposure are a potent combination of risk factors in the pathogenesis of COPD. While these studies focused on direct exposure to cigarette smoke, the effect of passive cigarette smoke exposure and occupational exposure are less well defined. The MZ genotype in conjunction with cigarette smoke exposure modifies a MZ heterozygote’s longitudinal decline in lung function following occupational exposure to vapours, dusts, fumes and gases [61]. An accurate estimate of the effect of passive cigarette smoke exposure on MZ individuals has yet to be determined but the harmful effect of environmental tobacco smoke was found to be greater in MZ schoolchildren [62].
The recent advances in our understanding of COPD risk in MZ individuals make it more important than ever to test individuals for AATD. Knowledge that the MZ genotype can significantly interact with environment to influence susceptibility to COPD is a powerful message and this should help deter heterozygotes from exposing themselves to potentially harmful environmental risk factors. The timely detection of at risk MZ individuals underpins the importance of diagnosing this condition early in order to reduce smoking initiation rates [63] and also increase smoking cessation [64].

2.6. AATD heterozygosity: A biological perspective

Analysis of sputum from non-smoking asymptomatic MZ individuals without evidence of airflow obstruction demonstrates increased neutrophil counts and IL-8 levels compared with MM individuals [65]. This indicates that the co-expression of the Z allele could have pro-inflammatory consequences. Harbouring the Z mutation may confer a survival advantage as the formation of polymers at sites of inflammation could potentially focus and amplify the immune response to aid the eradication of invading pathogens [66]. However, this advantage is abolished by environmental exposure to cigarette smoke via enhanced polymerization of the Z protein which potentiates a deleterious pro-inflammatory milieu in the AAT deficient lung, culminating in an increased risk of developing COPD [67].

The observed increased risk of COPD in MZ smokers challenges some of the underlying tenets of the protease-antiprotease theory. Given that MZ individuals have intermediate levels of circulating AAT, it is biologically plausible that an imbalance in pulmonary neutrophil elastase and a suboptimal protective level of AAT may be responsible for the observed increased risk of airflow obstruction and COPD in MZ heterozygotes. Reactive oxygen species in cigarette smoke can inactivate pulmonary AAT on the one hand and also promote a pro-inflammatory environment by increasing neutrophilic influx into the lung by the promotion of polymerisation of Z AAT on the other [68]. The biological mechanism by which cigarette smoke is presumed to enhance the risk of COPD in MZ heterozygotes is summarised in Figure 2.

The increased risk of COPD in MZ heterozygotes should lead to a reconsideration of what is the true protective threshold. This has implications not only for our understanding of the pathogenesis of COPD but also for AAT replacement therapy. Plasma purified AAT has been administered for almost 30 years by intravenous infusion to severe AATD individuals [69] with the aim of maintaining the plasma levels of AAT above the 11 µM level (approximately 0.56 g/l) throughout the duration of therapy [70]. The conflicting results and the paucity of clinical evidence for AAT replacement therapy [71] in severe AAT deficiency (ZZ) may be the result of targeting a sub-therapeutic threshold and augmenting the threshold to a higher MZ level may lead to improved treatment efficacy. The original threshold was based on mean AAT plasma concentration in the SZ phenotype as these individuals were thought to rarely develop COPD [72]. The SZ phenotype is more common than ZZ but studies in this area have been relatively few [73, 74]. However, an accurate determination of this risk would be very difficult as it would require a similar family based approach to that employed to determine the risk in MZ individuals including rigorous control for cigarette smoke exposure and a number of different patient groups encompassing the Z, S and M alleles. Until such information is
available it may be prudent to consider a new protective threshold as MZ individuals are not likely to develop lung disease in the absence of cigarette smoke exposure.

The emerging weight of evidence regarding the risk of COPD in MZ heterozygotes raises several important questions for further research. Firstly, what are the biological mechanisms by which cigarette smoking confers MZ heterozygotes with an increased risk of COPD? Secondly, in a longitudinal family based study, does the slope of lung function decline differ significantly between MZ and MM first degree relatives? What is the true protective threshold level of AAT and would increasing this threshold level result in greater therapeutic efficacy of AAT augmentation therapy?

2.7. When does AATD present – An Irish perspective

Trends in diagnosis and clinical presentation of severe AATD individuals in Ireland were recently investigated in a study of ZZ individuals enrolled in the Irish National AATD Registry. A total of 120 ZZ AATD individuals attending the national AATD centre completed a detailed questionnaire. For the entire group, the mean age of reported symptom onset was 37.8+/-1.6 years (range 0.03-80) while the mean age at diagnosis was 44.1+/-1.6 years (range 0.03-80). This leaves a mean interval between reported onset of first symptoms and diagnosis of AATD of 6.5+/-1.0 years (range 0 – 46). However, when subjects identified through family screening were excluded, the diagnostic delay increased to 8.5+/-1.2 years (range 1 – 46). In
addition, the average number of physicians seen by the entire group prior to a diagnosis of AATD was 3 (range 1 – 13). The findings are similar to data from other registries and reflect the diagnostic odyssey that individuals are often subjected to before a correct diagnosis is reached [6, 28, 75]. This further highlights the under-recognition of AATD that persists.

2.8. Who should be tested?

Guidelines published by the World Health Organisation (WHO) and the American Thoracic Society/European Respiratory Society (ATS/ERS) recommend the establishment of targeted screening programmes for the detection of individuals with AATD [3, 4]. In comparison to general population screening which can be more difficult and expensive to perform, targeted detection programmes offer a much higher rate of detection and are significantly more cost effective. The Irish National AATD Targeted Detection Programme began in 2004 and follows the ATS/ERS and WHO guidelines for the diagnosis of AATD. The ATS/ERS guidelines recommend targeted screening of patients with COPD, non-responsive asthma, cryptogenic liver disease and also first-degree relatives of known AATD individuals, termed type A recommendations (Table 2).

### ATS/ERS Recommendations for Diagnostic Testing (Type A)

<table>
<thead>
<tr>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults with symptomatic emphysema or COPD (regardless of age or smoking history)</td>
</tr>
<tr>
<td>Adults with asthma with airflow obstruction that is incompletely reversible after aggressive treatment with bronchodilators</td>
</tr>
<tr>
<td>Asymptomatic individuals with persistent obstruction on pulmonary function tests with identifiable risk factors (e.g. cigarette smoking, occupational exposure)</td>
</tr>
<tr>
<td>Adults with necrotising panniculitis</td>
</tr>
<tr>
<td>Siblings of individuals with AATD</td>
</tr>
<tr>
<td>Individuals with unexplained liver disease, including neonates, children, and adults, particularly the elderly</td>
</tr>
</tbody>
</table>

**Table 2.** ATS/ERS recommendations for diagnostic testing for AATD (type A recommendations).

In addition to these groups, ATS/ERS guidelines also recommend testing should be considered in a number of other scenarios as outlined in table 3 (type B recommendations).

### ATS/ERS Recommendations for Diagnostic Testing (Type B)

<table>
<thead>
<tr>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults with bronchiectasis without evident etiology</td>
</tr>
<tr>
<td>Adolescents with persistent airflow obstruction</td>
</tr>
<tr>
<td>Asymptomatic individuals with persistent airflow obstruction and no risk factors</td>
</tr>
<tr>
<td>Adults with C-ANCA-positive (anti-proteinase 3-positive) vasculitis</td>
</tr>
</tbody>
</table>

**Table 3.** ATS/ERS recommendations for diagnostic testing for AATD (type B recommendations).
3. How do we test for AATD?

The laboratory diagnosis of AATD is usually performed by following two steps; determination of AAT concentration in serum or plasma (quantitative) and identification of allelic variants by phenotyping or genotyping (qualitative) [76-78]. Quantification of AAT is generally the first investigation and has the advantages of being quick and relatively inexpensive. Clinically, a simple rule of thumb is the lower the level of AAT, the higher the risk of COPD. AAT quantification is routinely performed in most clinical chemistry, biochemistry, and immunology hospital laboratories. If quantification of AAT reveals a level below a pre-determined cut-off point or threshold (for example 1.0 g/l or 100 mg/dl) the sample should be automatically reflexed to phenotyping [79, 80]. This is the most cost-efficient and prudent algorithm. If necessary, genotyping using allele-specific PCR (usually to Z and S) and/or direct sequencing of the AAT gene can be performed either as a further investigation or on a complementary basis. The choice of using phenotyping or genotyping depends on resources available and the type of sample being referred, and there are advantages and disadvantages associated with both qualitative methods.

3.1. AAT quantification

AAT levels are measured routinely by immunoassay techniques such as nephelometry and turbidimetry, or less commonly by radial immunodiffusion [81, 82]. AAT levels measured in our centre are determined using immune turbidimetry on an Olympus AU540 analyser. The WHO and ATS/ERS guidelines recommend that AAT levels should be measured at least once in COPD patients. Although a substantial correlation between AAT phenotype and circulating
AAT concentrations has been established by several groups [70, 80, 83], confounding factors include normal intra-individual variation, depression of AAT production in liver disease, malnutrition, and the fact that AAT is an acute phase protein [84, 85]. Potential analytical variation may also occur; however, this variation is generally not significant. The increasing availability of external quality assurance schemes and accreditation programmes has led to improvements in testing accuracy, sensitivity, and reproducibility. In terms of which type of blood sample to use for AATD testing, a study by Miles et al in 2004 [86] which compared results from serum and heparinised plasma samples for 45 different chemistry tests addressed this concern. No statistically significant difference was observed in AAT concentrations measured in serum compared to plasma.

As an acute phase reactant, AAT levels are increased during the acute phase response, for example during infection or surgery [13]. Therefore, markers of inflammation such as CRP should be considered when assessing the concentration of AAT, and this has been discussed comprehensively elsewhere [87]. If CRP is indeed elevated, the quantification of AAT should be repeated once the acute phase response has subsided. The acute phase response will however, not result in a significant increase in AAT level in severe AATD (e.g. ZZ, Z/null). In contrast, AAT levels in heterozygotes (e.g. MZ, SZ) can be falsely elevated to levels similar to those observed in MM individuals, masking the underlying deficiency. For this reason, quantification of AAT levels alone is not a definitive test, and is no substitute for phenotype or genotype analysis, neither of which is affected by the acute phase.

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Cases</th>
<th>Mean AAT (g/l +/- SEM)</th>
<th>Range AAT (g/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS</td>
<td>1209</td>
<td>1.23 +/- 0.01</td>
<td>0.40 – 3.82</td>
</tr>
<tr>
<td>MZ</td>
<td>1657</td>
<td>0.91 +/- 0.01</td>
<td>0.44 – 4.08</td>
</tr>
<tr>
<td>SS</td>
<td>60</td>
<td>0.91 +/- 0.01</td>
<td>0.56 – 1.54</td>
</tr>
<tr>
<td>SZ</td>
<td>165</td>
<td>0.65 +/- 0.01</td>
<td>0.35 – 1.17</td>
</tr>
<tr>
<td>ZZ</td>
<td>219</td>
<td>0.25 +/- 0.001</td>
<td>0.11 – 0.61</td>
</tr>
</tbody>
</table>

Table 4. Mean AAT in deficient phenotypes identified in the Irish National AATD Targeted Detection Programme.

In the formulation of diagnostic algorithms for AATD the cut-off or threshold AAT value is critical to effective screening efforts and the identification of at risk individuals. A study by Donato et al in 2012 found a cut-off of 1.0 g/L was sufficient for the detection of severe (ZZ, Z/null) and intermediate AATD (e.g. MZ and SZ heterozygotes) [79]. Intermediate AATD has been an area of some controversy, with previous guidelines adopting stringently low cut-off values (for example 0.6 g/l) which would fail to detect large at risk populations of intermediate AATD. We know now that SZ and MZ individuals are also at risk of lung disease, particularly if they smoke [59, 74], and this knowledge has led to a change in diagnostic algorithms and increased the heterozygote detection rate. In light of the Donato study and our own data from screening 12,000 individuals we employ a cutoff point of 1.0 g/l at our centre as this is optimal...
for the detection of severe and intermediate AATD. Using this cut off value reduces laboratory costs and unnecessary testing, while maximising the detection of at risk individuals. An exception where a cut off value may not apply is when screening individuals due to a family history of AATD, as in this case it should be recommended the phenotype is checked regardless of AAT level.

3.2. AAT phenotyping

The ATS/ERS guidelines identify serum phenotyping as the ‘gold standard’ for the diagnosis of AATD. The qualitative detection and characterisation of AAT variants is carried out in our centre by isoelectric focusing followed by immunofixation using a kit which is the only FDA-approved method for AAT phenotype determination [88]. The isoelectric focusing (IEF) method on agarose gel has an added immunofixation step which utilises a specific antibody to AAT. This renders it superior to traditional IEF techniques due to its high resolution and reproducibility. IEF is also advantageous due to the fact it can easily detect rare and novel phenotypes. IEF identifies the various isoglycoforms and highlights the microheterogeneity of AAT in terms of carbohydrate side chains, but more importantly highlights the macroheterogeneity of AAT in terms of genetic variation. AAT phenotype is determined by comparison to three reference standards (e.g. MM, MS, and ZZ) and by visual inspection by a minimum of two independent observers. All IEF results are checked and correlated with the corresponding AAT levels. The recent publication of a reference compendium of known AAT phenotypes is a helpful resource for interpreting IEF migration patterns of AAT variants [89].

Figure 4. IEF migration pattern of common (left) and rare (right) AAT phenotypes identified in Ireland.
There are some cases in which analytical errors may occur using the IEF technique. Patients who are on augmentation therapy receive intravenous administration of purified AAT (isolated from MM donor individuals). The M variant will be detected in samples obtained from individuals receiving therapy and could result in discordant or unidentifiable migration patterns (e.g. a ZZ individual on therapy may appear MZ). Another error is possible with the presence of null mutations, which are a class of mutations characterised by a total absence of AAT secretion. Therefore, heterozygote null cases such as M/null, Z/null, S/null will appear as homozygous MM, ZZ, SS respectively [90, 91]. M/null and S/null phenotypes can be identified by the lower than expected AAT level. More difficult to identify are the Z/null phenotypes as the AAT level in ZZ compared to Z/null phenotypes is so low as to be practically indistinguishable. Similarly, caution must be taken with samples from individuals following a blood transfusion; this may also result in an incorrect diagnosis due to the possibility of the phenotype of the donor being present. If necessary genotyping using PCR and/or direct sequencing of the SERPINA1 gene can be achieved either in a complementary investigation to investigate discordant results or to identify rare and novel phenotypic variants.

3.3. AAT genotyping and sequencing

The adoption of dried blood spot (DBS) samples in an attempt to increase testing rates by making sampling easier, coupled with advances in molecular diagnostics, has resulted in the development of genotyping assays for AATD. Genotyping assays are commonly performed by melt curve analysis on real-time PCR instruments with primers and probes designed for specific mutations or less frequently by PCR-based restriction fragment length polymorphism (RFLP) analysis [92, 93], although RFLP methods have been replaced by the faster and more efficient melt curve methods. Allowing for the fact the DBS method has the convenience of allowing home testing and easier transportation of samples [94], in our centre we encourage the collection of serum or plasma samples for phenotyping by isoelectric focusing. This is primarily due to the nature of the sample referral centres which are large hospitals with specialist respiratory clinics, and also due to cost and logistical reasons.

Genotyping has the advantage of facilitating the rapid screening of both dried blood spots and DNA isolated from blood and is arguably less prone to interpretation errors which may occur with phenotyping. A downside to the method is that many laboratories, generally for cost and logistical reasons, employ primers for selected mutations, often the most common Z and S. In some cases, this can lead to rare mutations such as I, F, and M\textsubscript{malton} not being detected and misclassified as normal [90]. For this reason, in certain laboratories the genotyping method is used on a complementary or a clarification basis, unless specific M primers are being used.

For the precise identification of rare and unusual phenotypes observed in our centre we reflex to sequencing the gene for AAT (SERPINA1, RefSeq: NG_008290). This involves the isolation of DNA and sequencing the coding exons (II-V) of the SERPINA1 gene [95]. The detailed genetic analysis has led to the identification and characterisation of many rare and novel SERPINA1 alleles (Table 5).
Table 5. Common and rare pathological AATD variants detected in Ireland.

<table>
<thead>
<tr>
<th>Variant</th>
<th>Mechanism</th>
<th>Effect</th>
<th>Disease Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z</td>
<td>GAG – AAG, Glu342Lys</td>
<td>Polymerisation, impaired secretion and severe deficiency</td>
<td>Lung &amp; liver</td>
</tr>
<tr>
<td>S</td>
<td>GAA – GTA, Glu264Val</td>
<td>Impaired secretion and mild deficiency</td>
<td>Lung &amp; liver (in compound heterozygotes e.g. SZ)</td>
</tr>
<tr>
<td>I</td>
<td>CGC – TGC, Arg39Cys</td>
<td>Impaired secretion and mild deficiency</td>
<td>Lung &amp; liver (case reports in compound heterozygotes e.g. IZ)</td>
</tr>
<tr>
<td>F</td>
<td>CGT – TGT, Arg223Cys</td>
<td>Defective protease inhibition</td>
<td>Lung (case reports in compound heterozygotes e.g. FZ)</td>
</tr>
<tr>
<td>Null (Q0)</td>
<td>Mutations causing gene deletion, premature stop codon or mRNA degradation</td>
<td>No AAT produced</td>
<td>Lung</td>
</tr>
<tr>
<td>M_malton</td>
<td>ΔTTC, ΔPhe52</td>
<td>Polymeration, impaired secretion and severe deficiency</td>
<td>Lung &amp; liver</td>
</tr>
<tr>
<td>Z_bristol</td>
<td>ACG – ATG, Thr85Met</td>
<td>Intracellular accumulation &amp; defective glycosylation</td>
<td>Lung</td>
</tr>
<tr>
<td>M_wurzburg</td>
<td>CCC – TCC, Pro369Ser</td>
<td>Block in secretion</td>
<td>Lung &amp; liver</td>
</tr>
</tbody>
</table>
4. Why should we test?

There are clear benefits to a diagnosis of AATD for the clinician and the individual. Unfortunately, these benefits are often ignored to the detriment of the affected individual and the extended family.

4.1. Smoking cessation and occupational exposure considerations

The deleterious consequences of smoking on lung health in general and on the lungs of individuals with AATD in particular are well known and the origins of this can be traced back to the late 1960s. The twin discoveries of AATD and its association with COPD [16], and the induction of emphysema by the protease neutrophil elastase (NE) [96] led to an explosion in research surrounding proteolysis and lung disease. Importantly, NE was found to be exquisitely sensitive to inhibition by AAT by Aaron Janoff in 1968 [97]. The pathological effects of smoking were further elucidated when it was found products of cigarette smoke were able to destroy the anti-NE activity of AAT [98]. Despite being an excellent inhibitor of NE, the active site methionine residue at position 358 of the AAT molecule is easily oxidised by cigarette smoke and oxidants released by immune cells [99-101]. These studies provided the clear and irrefutable evidence that smoking causes a functional deficiency in the antiprotease screen. Therefore, in those individuals who develop COPD solely due to smoking, this functional deficiency contributes to the pathogenesis of disease. In individuals with AATD who develop COPD, the deficiency which contributes to the pathogenesis of disease is genetic.

So, we know that the small and precious quantity of AAT that does eventually reach the lung in ZZ individuals is knocked out by cigarette smoke. This is the reason why AAT deficient individuals who smoke develop early onset lung disease [102]. Cigarette smoke is by far the single most important risk factor for the development of COPD in AATD individuals [103-105].

In fact, smoking can reduce the life expectancy of a ZZ patient by up to 25 years [102]. Carpenter et al in a 2007 study revealed higher smoking cessation rates in individuals with a diagnosis of AATD compared to COPD individuals [64]. In this study severely deficient individuals (ZZ and SZ) had a 59% quit attempt rate, compared to a 26% quit attempt rate in unaffected MM individuals. This information is vital in the clinic as it shows that knowledge of AATD motivates the affected individual toward smoking cessation. Every ZZ, SZ, and MZ AATD individual should be educated about the incredibly harmful effects of cigarette smoke in AATD. Smoking cessation and the avoidance of occupational and environmental exposures (for example particulate matter, chemical vapours, and agricultural dusts) is paramount.

AATD individuals without apparent lung disease should also be encouraged to quit smoking as this cohort offers the most realistic chance of delaying or possibly preventing the development of COPD. A decision to quit smoking is the most important decision a person with AATD can make. The decision to modify this behaviour is strongly influenced by the quality of the information provided and how this is communicated to at risk individuals.

Ireland is a leader in Europe in terms of anti-smoking measures with the introduction of the first ban on smoking in the workplace [106]. However, a 2007 Irish Government study (Slán 2007 Survey of Lifestyle, Attitudes and Nutrition in Ireland) found that 34% of Irish 30 – 44
year olds currently smoke and this is the age bracket that AATD individuals first begin to report deterioration in lung health. To assess the effect of smoking on lung health in AATD we analysed lung function data from 120 ZZ individuals enrolled in the Irish National AATD Registry and correlated this to smoking history. While the relative contribution of occupational exposures was not taken into account, the mean FEV1 (% predicted) and diffusion capacity of carbon monoxide (DLCO, % predicted) was significantly higher in ZZ subjects who never smoked compared to ZZ subjects who were past or active smokers (Figure 6). This clearly demonstrates the destructive consequences of smoking for ZZ individuals.

Interestingly, smoking cessation rates were also analysed as part of this study. In the past smokers cohort 36% stopped smoking within the first 12 months after AATD diagnosis; 24% stopped smoking after the first 12 months post-AATD diagnosis and 40% had already stopped smoking prior to AATD diagnosis. This supports the findings of the earlier Carpenter study and demonstrates the positive effect of AATD diagnosis on smoking cessation rates.

### 4.2. Family screening

The area of family screening offers the greatest possibility for the prevention or at least postponement of COPD [107]. An early diagnosis of AATD provides tantalising opportunities for behaviour modification and lifestyle changes, the single most important of which is smoking cessation. Interim data from the Irish National AATD Registry demonstrates that ZZ
individuals detected by family screening tend to have preserved lung function compared to those identified by symptomatic screening (Figure 8).

Figure 7. DLCO (% predicted) stratified by smoking in ZZ individuals enrolled in Irish National AATD Registry (**p < 0.0001, *p < 0.05, t-test).

Figure 8. FEV1 (% predicted) in ZZ individuals diagnosed by symptomatic screening versus those diagnosed by family screening enrolled in Irish National AATD Registry (**p < 0.001, t-test).
An excellent example of the family screening possibilities opened up by a diagnosis of AATD is presented in a large family study from the Irish AATD Registry (Figure 9). In this example, the index case was diagnosed with AATD because of lung disease. Six of the nine siblings were subsequently tested revealing 3 ZZ individuals, 2 MZ individuals, and 1 MM individual.

Figure 9. Identification of ZZ proband (red arrow) and subsequent identification of at risk relatives by family screening.

4.3. Liver assessment

A baseline liver assessment should be performed in a newly-diagnosed AATD individual to investigate the presence of liver abnormalities. The primary tools for assessment are liver function tests and abdominal ultrasound. This is a practice not routine in the specialist respiratory clinic and ignorance of AATD and the potential for liver disease can be fatal. Early recognition is important for two reasons. The first reason is to prevent, recognize, and treat early the complications of AATD-related liver disease, which can include portal hypertension, encephalopathy, and tumours [108]. The second reason is to advise the patient to avoid injurious habits, such as alcohol consumption, which can accelerate disease. Interestingly, patients who undergo liver transplantation for other causes have a higher incidence of being heterozygous for AATD than the general population [40].

4.4. Vaccination

Influenza and pneumococcal vaccinations are recommended for all individuals with AATD [4]. A 2007 study investigated the practice of vaccinations and respiratory outcomes in AATD individuals in the USA and found over 80% of AATD individuals had received adequate influenza and pneumococcal vaccinations during the influenza season [109]. However, there was no significant difference in severity or rate of exacerbations between vaccinated and
unvaccinated individuals but the authors concluded that the vaccinated group may represent ‘sicker’ AATD individuals. Influenza and pneumococcal vaccinations in COPD patients are recommended in several guidelines for COPD [110, 111] and the unique susceptibility of AATD individuals provides additional motivation for vaccination, especially during influenza season.

4.5. Exacerbation management

Exposure to bacterial and viral infections can result in a respiratory exacerbation. Symptoms include increased dyspnoea, cough, and production of sputum [112]. The aggressive treatment of infections is recommended in AATD individuals as per ATS/ERS guidelines [4]. This is particularly important as frequent exacerbations have been shown to be related to worsening health-related quality of life (HRQoL). An English study investigated health status in AATD individuals over 12 months and recorded exacerbations, lung function and HRQoL. The authors concluded exacerbations occur commonly in AATD individuals and correlate to worse health status. Exacerbations were associated with a decline in the gas transfer of the lung for carbon monoxide over time (DLCO), but not FEV1 [113]. Interestingly, a study investigated exacerbation frequency in AATD individuals with COPD who were receiving augmentation therapy and found subjects with frequent exacerbations had the worst baseline HRQoL scores, as well as more physician visits and hospitalizations. Unfortunately, AATD individuals not receiving augmentation therapy were not included for comparison [114]. A recent longitudinal study undertaken in the USA, evaluated the effectiveness of a disease management and prevention programme for AATD individuals and involved 905 individuals over a 2 year period. The programme included written educational material for self-study and individualised treatment plans for exacerbations. Improved compliance was observed in the use of bronchodilators, oxygen therapy, and steroids during exacerbations. The management programme significantly reduced medical visits and showed a slower deterioration of HRQoL during exacerbations [115]. A follow-up study providing additional evidence to evaluate the long-term benefits of an AATD disease management programme would be beneficial.

4.6. Augmentation therapy

Augmentation therapy is the only specific therapy available for severe AATD, and comprises of intravenous administration of AAT derived from human plasma [116]. This treatment is available in several European countries and the USA [117]. The therapy comprises of weekly or fortnightly intravenous infusions of AAT preparations that augment the low levels of circulating AAT in severe AATD. However, its efficacy remains to be definitively proven and uncertainty persists concerning the therapy’s cost effectiveness [118]. Ongoing randomised clinical trials are being performed to definitively assess the efficacy of the treatment. Previous trials have been under-powered and have mostly demonstrated only biochemical efficacy with AAT levels restored to above the putative threshold in the blood and lung, with a failure to show clear clinical efficacy in randomised controlled trials [71, 119]. Nevertheless, there is evidence that augmentation therapy can slow lung function decline in AATD individuals, and moderately obstructed cohorts are most likely to benefit [120].
4.7. Pulmonary rehabilitation

Pulmonary rehabilitation is a tailored exercise programme aimed at restoring the best possible quality of life in patients with lung disease, particularly focused on reducing breathlessness, as well as improving independence and the physical ability to tolerate stress [121]. It is defined as a complex, multimodal treatment regimen for patients with pulmonary diseases [122]. The goal is to help patients become more physically active, to learn more about their disease, treatment options, and how to cope. Patients are encouraged to become actively involved in providing their own health care, more independent in daily activities, and less dependent on health professionals and expensive medical resources. Rather than focusing solely on reversing the disease process, rehabilitation attempts to reduce symptoms and reduce disability from the disease. In general, patients with COPD secondary to AATD tend to be younger compared to patients with usual COPD, and less comorbidity is observed. This suggests the potential for greater improvement in AATD individuals participating in rehabilitation programmes.

5. Why is testing not taking place?

The reasons for the continuing under-diagnosis of AATD are diverse and can include low medical and public awareness, the misconception that it is a rare disease, the belief that testing is complicated and expensive, and testing fatigue [123]. Current data suggests that less than 10% of individuals with severe AATD have been recognised globally [124], and increasing detection rates is the most pressing, and vexing issue for leaders in the AATD community. Unfortunately, some clinicians adopt the attitude of “what difference does a diagnosis of AATD actually make”. This is a challenge for all stakeholders and the benefits of AATD testing must be clearly stated in a simple powerful message to lung health professionals and policy-makers. In particular, the potential economic benefits are not being stressed enough [125]. Early diagnosis of AATD is an example of preventative medicine. The newly-diagnosed individual and healthcare provider have the power to arrest or prevent the development of COPD through lifestyle choices, close medical observation, and focused treatment. This in turn means that the long term financial burden on the health system is reduced and by remaining healthy the individual continues to contribute to society and the exchequer. There is also the consideration of the large direct medical cost to the symptomatic AATD individual [125]. So why does testing in COPD cohorts not occur if the ATS/ERS and WHO guidelines are so clear and the benefits so convincing?

Many early guidelines for AATD advocated testing early-onset COPD patients and this fallacy was to the detriment of screening efforts. The age at which manifestations of airway obstruction, pulmonary emphysema, or chronic bronchitis appear in ZZ individuals is highly variable [102]. While a common feature of AATD is indeed early-onset COPD, a significant AATD cohort do not develop symptoms until much later in life, particularly if non-smokers [126, 127]. In fact, among never-smokers the risk of liver disease increases with age in ZZ individuals [127, 128]. Numerous case reports have described AATD in elderly individuals with COPD who were lifelong never smokers [129]. Taken together, it is clear that screening for AATD
should be automatically performed in all COPD regardless of age or smoking history, especially as failure to do so has serious clinical repercussions for undiagnosed family members.

The fear of genetic discrimination, financial concerns, and privacy concerns are real barriers to testing for AATD in the COPD population [130]. Fears of genetic discrimination have been allayed in recent years with preventative legislation enacted in several countries, including Ireland and the US. Genetic discrimination was made illegal in Ireland from December 31st 2005 when the Irish government enacted new legislation. It became illegal to use or process the results of genetic testing for insurance, life assurance or mortgage purposes. This also applies in the case of employment, health insurance and occupational pension. What is assessed when a person is being considered for a financial product or insurance policy are the usual criteria including health history (symptom-related questions), lifestyle choices (smoking, alcohol, etc.), and the regular questions surrounding family history of particular illnesses. There are still reasons to be wary in this area. Following the advent of the Genetic Information Non-Discrimination Act (GINA) in the US in 2008, discrimination can be implicit, indirect and subtle, rather than explicit, direct and overt; and as a result can be harder to prove [131].

6. How can we increase detection of AATD?

Initiatives to increase detection rates might include automatic physician alerts suggesting AATD testing on pulmonary function test reports of patients with fixed airflow obstruction [132], better medical and patient education in the area of AATD [133], changes to national COPD guidelines, and a red flag to recommend testing for AATD on laboratory reports of patient with low AAT levels. The advent of finger-prick tests using dried blood spots (DBS) as a source of DNA has allowed home testing for AATD, with easier transportation of samples.

<table>
<thead>
<tr>
<th>Reasons why testing for AATD is not taking place.</th>
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<tbody>
<tr>
<td>Belief that AATD is a rare disorder</td>
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<tr>
<td>Perception that only early-onset non-smokers are affected</td>
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<tr>
<td>Therapeutic nihilism due to lack of specific treatments</td>
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<tr>
<td>Fear of genetic discrimination</td>
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<tr>
<td>Lack of education and awareness (in healthcare professionals &amp; public)</td>
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<tr>
<td>Testing fatigue</td>
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<tr>
<td>Failure to admit lack of knowledge</td>
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<td>Reluctance to lose patients to specialist centres</td>
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<tr>
<td>Lack of communication between clinicians and laboratory scientists</td>
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<tr>
<td>Absence of effective national guidelines</td>
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<tr>
<td>No access to testing methods</td>
</tr>
<tr>
<td>Privacy concerns</td>
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<tr>
<td>Perceived stigma</td>
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Table 6. Reasons why testing for AATD is not taking place.
to the laboratory [94]. This method of testing eliminates the fear of needles for the individual, and is also cheaper as the test does not require a visit to a general practitioner.

<table>
<thead>
<tr>
<th>Improve education in undergraduate and postgraduate medical and scientific training</th>
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<tbody>
<tr>
<td>Include primary care physicians and hepatologists in awareness efforts</td>
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<tr>
<td>Educate and empower respiratory nurse specialists</td>
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<tr>
<td>Public awareness campaigns</td>
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<tr>
<td>Patient empowerment</td>
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<tr>
<td>Update WHO and ATS/ERS guidelines for AATD</td>
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<tr>
<td>Refine COPD guidelines to include automatic testing for AATD</td>
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<tr>
<td>Laboratory red-flags</td>
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<tr>
<td>Pulmonary function test red-flags</td>
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<tr>
<td>Electronic health record prompts</td>
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<td>Embed as routine test by creating COPD care templates and physician order reminders</td>
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<tr>
<td>Joint seminars between pulmonologist and laboratory scientists</td>
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<tr>
<td>Presentations at national conferences</td>
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<tr>
<td>Provision of free testing kits</td>
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</table>

**Table 7. Strategies to improve the detection of AATD.**

An attractive strategy is the use of electronic red-flags on low AAT laboratory reports. This prompts the clinician to investigate low AAT results and reflex to phenotyping and/or genotyping. During our efforts to increase awareness at a national level in Ireland, we have advocated that hospital laboratories should include the following recommendation on AAT reports; “Serum AAT < 1.0 g/L may indicate alpha-1 antitrypsin deficiency and further investigation is recommended. Information is available from the Alpha One Foundation on www.alpha1.ie. AAT is an acute phase reactant and serum concentrations can increase significantly during trauma, acute infection or surgery.” This cost-neutral approach has been successfully implemented at 9 large hospitals in Ireland and has directly led to increased diagnosis of AATD in these centres and surrounding hinterlands. Implementation was achieved by presenting to lung specialists and laboratory scientists on site, and in the same room. This twin track approach is most effective and it is often the first time for each party to meet – those requesting the test and those performing the quantitative AAT assay. The aim is to eliminate missed diagnosis of AATD when a low AAT is reported but not acted upon. A particularly striking aspect of this strategy is that incidental findings of AATD are common, and hitherto asymptomatic cases can be detected. As AAT is an acute phase protein and a robust marker of inflammation, the test can...
be requested during routine blood work with the expectation that it will be dramatically increased. However, the opposite is sometimes the case. The inadvertent low finding is highlighted by the electronic red-flag and the ensuing diagnosis of AATD is the positive outcome. We are hopeful that this system will eventually be adopted on a nationwide basis and are in consultation with the government and various stakeholders to effect this change.

Figure 10. Example of a laboratory red-flag on low AAT results from a biochemistry laboratory at a large Irish hospital.

In the era of the electronic medical record, technology can help deliver or enhance specific clinical practices, such as testing for AATD. For example, if physicians were prompted to consider this condition when they received the results of pulmonary function tests (PFT) showing fixed airflow obstruction, testing for AATD should increase. Also, if eliciting a family history of COPD or chronic liver disease prompted a physician alert on the electronic medical record to test the serum AAT level, testing could increase. For example, a small pilot study found that the frequency of AATD testing increased when a prompt to test for AATD was included on the PFT reports of patients with airflow obstruction [132]. Another similar study looked at the impact of a clinical decision support system within an electronic health record which facilitated testing for AATD [134]. The alert within the electronic health record resulted in a four-fold increase in testing for AATD.
7. Other strategies

There are a host of other strategies which could lead to increased detection of AATD. These include continuing medical education lectures, AATD teaching in medical school and clinical chemistry curricula, public awareness campaigns, lobbying of public health officials, and making available free testing kits. Moreover, the WHO and ATS/ERS guidelines need urgent updating. AATD is often relegated to a footnote in many clinical guidelines for COPD. A summary of the ATS and ERS document outlining standards for the diagnosis and treatment of patients with COPD published in 2004 mentions AATD once, stating that “patients presenting with airflow limitation at a relatively early age (4th or 5th decade) and particularly those with a family history of COPD should be tested for alpha-1 antitrypsin deficiency” [135]. Narrow definitions such as these are damaging to efforts to increase AATD detection. Another strategy to promote testing is to empower patients by providing free, high-quality, easy to understand information available, such as the information material prepared by the Alpha-1 Foundation (www.alpha-1foundation.org).

8. Conclusion

The fact that cigarette smoking is often a coincident historical finding in the assessment of COPD has probably contributed to the remarkable global under-diagnosis of AATD. For example, of the estimated 3,000 ZZ individuals on the island of Ireland, less than 10% have been diagnosed. Unfortunately for the clinician and the patient, testing for AATD is not routinely considered in the assessment of COPD. Any model for COPD diagnosis, assessment and management must include automatic testing for AATD as one of the first steps. Large variability exists in the clinical course of lung disease in AATD and therefore all COPD patients should be tested for AATD, regardless of age or smoking history. The under-diagnosis of AATD in COPD is a situation that must not be allowed to continue.

Acknowledgements

We thank all the AATD individuals attending our centre for their continued collaboration in research, awareness and detection efforts. The Irish National AATD Targeted Detection Programme is supported by funding from the Irish Government. We thank Dr. Ilaria Ferrarotti, Dr. Stefania Ottaviani, and Prof. Maurizio Luisetti from the University of Pavia for their continued assistance with rare and novel variant identification. We would like to thank John Walsh and Angela McBride of the Alpha-1 Foundation (USA) for their continued support and encouragement. Finally, we wish to thank Pat O’Brien and Emma Pentony in the Department of Chemical Pathology in Beaumont Hospital for help with sampling and turbidimetry.
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