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Title: The Irish national alpha-1 antitrypsin deficiency targeted detection programme

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Body: AAT deficiency (AATD) results from mutations in the SERPINA1 gene, classically presenting with early-onset emphysema and liver disease. The most common mutation responsible for AATD is the Z mutation. AAT deficiency is under-diagnosed and prolonged delays in diagnosis are common. ERS and ATS guidelines advocate the screening of all COPD, poorly-controlled asthma, and cryptogenic liver disease patients, as well as first degree relatives of known AATD patients. Over 10,000 individuals have been screened following ATS/ERS guidelines. AAT levels were determined by immune turbidimetry and AAT phenotyping was performed by isoelectric focussing. Rare and novel mutations were identified by DNA sequencing of the SERPINA1 gene. To date we have identified 150 ZZ, 160 SZ, 50 SS, 1500 MZ, 1000 MS, and over 70 individuals with clinically significant rare phenotypes (e.g. IZ, FZ, IS, Null, Mmalton). Almost 30% of the screened cohort contained at least 1 AAT mutation. A number of rare and novel SERPINA1 mutations have also been identified, including the first Irish individuals homozygous for a Null mutation and for the Mmalton mutation. Our results underline the need for increased awareness and early detection of AATD. All COPD patients should be tested for AATD, regardless of age or smoking history. The advantages of early and accurate diagnosis of AATD are manifold, particularly regarding pulmonary and liver surveillance, family member testing, smoking cessation, and consideration of occupational and environment exposures. Overall, our data demonstrates the high prevalence of AATD in Ireland and the efficacy of the targeted detection approach.