Detection of alpha-1 antitrypsin deficiency: A review

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Received 7 August 2008; accepted 4 October 2008
Available online 17 November 2008

Summary
Screening studies reveal a much larger number of individuals expected to have alpha-1 antitrypsin deficiency than is clinically recognized, with estimates that only about 2–10% of such individuals have been diagnosed. In the context that recognition of alpha-1 antitrypsin may prompt specific interventions (e.g., smoking avoidance, testing of family members, genetic counseling, and consideration of augmentation therapy), diagnosis is important, inviting much attention for efforts to identify affected individuals.

Strategies to identify affected individuals include both population-based screening and targeted detection, and available studies have employed both approaches, though large-scale population-based screening is challenging. As reviewed in this paper, targeted-detection studies have generally produced a higher rate of detecting disease, and tend to be more successful with easier sampling techniques. Strategies to enhance detection in targeted studies have included awareness campaigns, easy testing techniques (such as evaluation of dried blood spots and home, confidential testing), and inclusive criteria for testing which span the full spectrum of clinical manifestations of alpha-1 antitrypsin deficiency.

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Introduction

Alpha-1 antitrypsin deficiency (AATD) is an under-recognized condition with only a minority of affected individuals detected, long diagnostic delays between initial symptoms and diagnosis, and evidence that affected individuals may see many physicians with suggestive symptoms before an initial diagnosis is made.1-5 In the context that under-detection of AATD has been appreciated since at least the early 1990s,1-3,4 and that detecting AATD may prompt specific interventions (e.g., testing of family members, emphasis on smoking avoidance, and consideration of augmentation therapy),6 a variety of efforts have been undertaken to enhance recognition of individuals with AATD. The purpose of this paper is to review the issue of detecting individuals with AATD, both regarding evidence about the rates at which affected individuals are detected and the results of interventions undertaken to identify individuals with AATD.

Rates of detecting individuals with alpha-1 antitrypsin deficiency

Estimates suggest that fewer than 10% of Americans with severe AATD (defined as having serum levels below the protective threshold value of 11 μM) are recognized clinically,1,4,7 and that similarly low recognition rates have been observed in all countries in which the issue has been addressed.8

Focusing on the United States, extrapolation of data from population-based screening studies,9,10 evaluations of patients with COPD,11 and genetic epidemiologic surveys12 lead to convergent estimates of about 60,000–90,000 PI*ZZ Americans,4 of which only about 6000 have been identified.7

Several other studies confirm that individuals with severe AATD escape medical detection. In a study of the frequency of AATD in St. Louis, Silverman et al. sampled 20,000 blood specimens donated to the St. Louis blood bank and found 7 who had PI*ZZ deficiency. Extrapolation to a St. Louis population of 2 million individuals at the time predicted 700 affected individuals. However, only 28 could be identified (4%) after contact investigations.10

Reasoning that younger individuals with severe AATD may be asymptomatic and thus escape medical detection, Tobin et al. estimated that the majority of PI*ZZ subjects would present to a pulmonary physician between ages 45 and 54. In a multicenter survey undertaken by the British Thoracic Association in 1976, they found 90 PI*ZZ individuals in that age band.13 Yet, applying PI*ZZ prevalence estimates of 0.03% would have predicted 2000 PI*ZZ individuals in that age range, suggesting that only 4.5% were identified.13

Finally, combining data from the Alpha-1 International Registry,14 and from the U.S. Alpha-1 Foundation Research Network Registry,15 which together encompass 21 countries on 4 continents, indicates approximately 2350 registered individuals with the PI*ZZ phenotype. Yet, published genetic epidemiologic surveys estimate about 100,000 PI*ZZ individuals from those countries,16 suggesting that only 2.4% of individuals have been identified.

Taken together, available estimates from many countries consistently suggest that only a small minority of individuals with severe AATD (~2—10%) are recognized clinically. In the context of such under-recognition, a variety of efforts have been undertaken to detect such individuals.

Interventions to detect individuals with alpha-1 antitrypsin deficiency

Tables 1 and 2 summarize the results of studies undertaken to detect individuals with AATD. As shown, detection efforts have included both population-based, true screening studies, in which unselected groups without heightened suspicion of having AATD have been broadly tested (Table 1),9,10,17-20 and case-finding or targeted-detection efforts (Table 2),11,21-27 in which individuals have been tested because a heightened suspicion exists of their having AATD (e.g., either because of clinical manifestations, such as chronic obstructive pulmonary disease or cirrhosis, or because of a family history of AATD).

Screening studies

Of the 20 available screening studies listed in Table 1, the two largest population-based screening studies were conducted by O’Brien et al. in Oregon9 and Sveger in Sweden.28

O’Brien et al. screened 107,038 infants with blood specimens obtained from a heel stick and collected on filter paper on the day of discharge. A second sample was obtained in 75% of these same infants at 4–6 weeks of age. Abnormal screening results were repeated on all but 26 infants. The study identified 32 children with two or more abnormal screening tests: 21 with homozygous deficient phenotypes (ZZ or Z null) and 11 heterozygous for variant genotypes (including PI*MZ, PI*SZ and others that were not specified).9

In the largest available population-based screening study, Sveger screened 200,000 infants representing 95% of all infants born in Sweden between November 1972 and September 1974.28,29 Of the 200,000 screenees, the study identified 127 PI*Z individuals as well as 48 PI*SZ individuals.

Aggregating the results of the other 18 detection studies in Table 1 by region shows the following detection rates:
United States 12/38,280 (0.03%), Europe/Scandinavia 35/114,775 (0.03%), Africa 3/479 (0.63%) and Asia 0/856. As a corollary of these large population-based screening studies, important insights regarding the natural history of AATD have emerged from follow-up of the individuals identified as having PI \( \text{ZZ} \) AATD at birth. Specifically, in both the 15-year follow-up of individuals screened in Oregon,30 and in the 30-year follow-up of individuals screened in Sweden,31 individuals tested had normal lung function at mean ages of 15.1 and 30.6 years, respectively. Furthermore, the rate of cigarette smoking among AATD individuals was lower than that among age-matched peers,30 or the population as a whole.31

Targeted-detection studies

Various studies have undertaken targeted detection of individuals with alpha-1 antitrypsin deficiency using a variety of testing methods and target populations. For example, some studies have examined the prevalence of severe AATD among patients seen at single health care facilities,11,26 while others have conducted regional or national awareness campaigns with associated free testing.21,24,25,27 Still other studies have attempted to enhance detection of individuals with severe AATD by suggesting alpha-1 antitrypsin testing to clinicians receiving the results of pulmonary function tests showing airflow obstruction or by directly approaching patients whose pulmonary function tests are consistent with chronic obstructive pulmonary disease (COPD). The results of these various studies are listed in Table 2 and discussed below.

In an early study at the Sepulveda Veterans Administration Hospital, Lieberman et al. performed alpha-1 antitrypsin blood tests on 965 consecutive Veterans attending the COPD Clinic using a trypsin inhibitory capacity assay,11, and found that PI \( \text{ZZ} \) individuals comprised 1.9% of those tested.

In a second early study, Matzen et al. used crossed electrophoresis and serum trypsin inhibitory capacity assays to determine the phenotypes of 225 patients previously diagnosed as having severe pulmonary function tests showing airflow obstruction or by directly approaching patients whose pulmonary function tests are consistent with chronic obstructive pulmonary disease (COPD). The results of these various studies are listed in Table 2 and discussed below.

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Table 1 Prevalence estimates of specific alpha-1 antitrypsin deficiency phenotypes in selected population screening studies.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year of study</th>
<th>Location of study</th>
<th>Subject population</th>
<th>Number screened</th>
<th>Prevalence of specific AAT phenotype (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saris et al.19</td>
<td>1972</td>
<td>Finland</td>
<td>College students</td>
<td>664</td>
<td>ZZ 0.15, SZ 5.12, MZ 1.04, SS 0.05, MS 22.7, Other deficiency phenotypes</td>
</tr>
<tr>
<td>Goedde et al.47</td>
<td>1973</td>
<td>Spain</td>
<td>Population survey</td>
<td>576</td>
<td>ZZ 0.04, SZ 0.21, MZ 0.01, SS 0.4, MS 7.19</td>
</tr>
<tr>
<td>Vandeville et al.54</td>
<td>1973</td>
<td>Zaire</td>
<td>Population survey</td>
<td>132</td>
<td>ZZ 0.07, SZ 0.07, MZ 2.24, SS 0.28, MS 0.05, Other deficiency phenotypes</td>
</tr>
<tr>
<td>Webb et al.42</td>
<td>1973</td>
<td>New York</td>
<td>Population survey</td>
<td>500</td>
<td>ZZ 0.07, SZ 0.07, MZ 0.21, SS 0.29, MS 0.04, Other deficiency phenotypes</td>
</tr>
<tr>
<td>Cook46</td>
<td>1975</td>
<td>United Kingdom</td>
<td>Population survey</td>
<td>5588</td>
<td>ZZ 0.04, SZ 0.21, MZ 0.01, SS 0.4, MS 7.19</td>
</tr>
<tr>
<td>Hoffmann and van den Broek49</td>
<td>1976</td>
<td>Netherlands</td>
<td>Population survey</td>
<td>1474</td>
<td>ZZ 0.07, SZ 0.07, MZ 2.24, SS 0.28, MS 0.05, Other deficiency phenotypes</td>
</tr>
<tr>
<td>Lieberman et al.43</td>
<td>1976</td>
<td>California</td>
<td>High school students</td>
<td>1841</td>
<td>ZZ 0.27, SZ 1.85, MZ 0.05, SS 0.28, MS 0.05, Other deficiency phenotypes</td>
</tr>
<tr>
<td>Sveger28,29</td>
<td>1976</td>
<td>Sweden</td>
<td>Newborns</td>
<td>200,000</td>
<td>ZZ 0.06, SZ 0.02, MZ 0.23, SS 0.37, MS 0.03, Other deficiency phenotypes</td>
</tr>
<tr>
<td>Evans et al.44</td>
<td>1977</td>
<td>New York</td>
<td>Newborns</td>
<td>1010</td>
<td>ZZ 0.86, SZ 0.28, MZ 0.23, SS 0.37, MS 0.03, Other deficiency phenotypes</td>
</tr>
<tr>
<td>Harada et al.55</td>
<td>1977</td>
<td>Japan</td>
<td>Blood donors</td>
<td>856</td>
<td>ZZ 0.86, SZ 0.28, MZ 0.23, SS 0.37, MS 0.03, Other deficiency phenotypes</td>
</tr>
<tr>
<td>Massi and Vecchio53</td>
<td>1977</td>
<td>Somalia</td>
<td>Newborns</td>
<td>347</td>
<td>ZZ 0.86, SZ 0.28, MZ 0.23, SS 0.37, MS 0.03, Other deficiency phenotypes</td>
</tr>
<tr>
<td>Morse et al.45</td>
<td>1977</td>
<td>Tucson</td>
<td>Population survey</td>
<td>2944</td>
<td>ZZ 0.86, SZ 0.28, MZ 0.23, SS 0.37, MS 0.03, Other deficiency phenotypes</td>
</tr>
<tr>
<td>Klasen et al.50</td>
<td>1978</td>
<td>Italy</td>
<td>Hospital outpatients</td>
<td>202</td>
<td>ZZ 0.86, SZ 0.28, MZ 0.23, SS 0.37, MS 0.03, Other deficiency phenotypes</td>
</tr>
<tr>
<td>O’Brien et al.9</td>
<td>1978</td>
<td>Oregon</td>
<td>Newborns</td>
<td>107,038</td>
<td>ZZ 0.02, SZ 0.07, MZ 0.23, SS 0.37, MS 0.03, Other deficiency phenotypes</td>
</tr>
<tr>
<td>Dijkman et al.17</td>
<td>1980</td>
<td>Netherlands</td>
<td>Newborns</td>
<td>95,083</td>
<td>ZZ 0.03, SZ 0.07, MZ 0.23, SS 0.37, MS 0.03, Other deficiency phenotypes</td>
</tr>
<tr>
<td>Dykes et al.46</td>
<td>1984</td>
<td>Minnesota</td>
<td>Blood donors</td>
<td>904</td>
<td>ZZ 0.03, SZ 0.07, MZ 0.23, SS 0.37, MS 0.03, Other deficiency phenotypes</td>
</tr>
<tr>
<td>Kimpen et al.18</td>
<td>1988</td>
<td>Belgium</td>
<td>Newborns</td>
<td>10,329</td>
<td>ZZ 0.03, SZ 0.07, MZ 0.23, SS 0.37, MS 0.03, Other deficiency phenotypes</td>
</tr>
<tr>
<td>Silverman et al.10</td>
<td>1989</td>
<td>St. Louis</td>
<td>Blood donors</td>
<td>20,000</td>
<td>ZZ 0.03, SZ 0.07, MZ 0.23, SS 0.37, MS 0.03, Other deficiency phenotypes</td>
</tr>
<tr>
<td>Spence et al.20</td>
<td>1993</td>
<td>New York</td>
<td>Newborns</td>
<td>11,081</td>
<td>ZZ 0.03, SZ 0.07, MZ 0.23, SS 0.37, MS 0.03, Other deficiency phenotypes</td>
</tr>
<tr>
<td>Kaczor et al.51,52</td>
<td>2007</td>
<td>Poland</td>
<td>Random sample</td>
<td>859</td>
<td>ZZ 0.03, SZ 0.07, MZ 0.23, SS 0.37, MS 0.03, Other deficiency phenotypes</td>
</tr>
</tbody>
</table>

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In a study in which a mail awareness campaign was coupled with free testing for AATD (using a polymerase chain reaction blood spot test), Bals et al. sent mailings to all general practitioners and both pediatric and pulmonary specialists in Germany, established a web site, and announced the study at various national meetings. Of 17,688 test kits requested, 2722 were returned and 2696 were technically testable. Among these 2696, the overall prevalence of severe deficient phenotypes was 12.4% (including PI*ZZ e 9.9% and PI*SZ e 2.0%, Table 2).21

Campbell reported the results of an alpha-1 antitrypsin detection service which makes available free testing for AATD (immunoassay, isoelectric focusing, and polymerase chain reaction analysis for specific alleles) on clinicians’ submitting dried blood spot specimens. Between March 1991 and February 29, 2000, 30,631 samples had been submitted, of which 1021 (3.3%) were said to have been “diagnosed with the disease” (though the specific phenotype was not specified in the available report).32

de la Roza and colleagues reported their experience with a 2-phase case-finding program in Spain using both immunonephelometry and polymerase chain reaction testing of dried blood spot specimens for the Z and S alleles. In phase 1 of the program, of 971 samples collected from 7 pulmonologists who were encouraged to submit samples from their patients with COPD, 5 (0.5%) were found to be PI*ZZ. In phase 2 in which members of the COPD task force of the Spanish Society of Pneumology and Thoracic Surgery were encouraged to submit samples, 1166 samples were collected, of which PI*ZZ, PI*SS, and PI*SZ phenotypes were observed in 3 samples (0.3%) each. With both phases taken together, of 2137 samples collected, the PI*ZZ phenotype was found in 0.37% (N = 8).24

In a preliminary communication of a targeted-detection program in Florida reported by Brantly et al., of 969 samples analyzed, PI*ZZ specimens were found in 31 (3.2%), PI*SZ in 4 (0.4%), and PI*MZ in 107 (11%).22

Corda et al. reported the results of a targeted-detection program in an Italian hospital in which nephelometry and polymerase chain reaction assays were performed when patients presented with the following suggestive diagnoses: emphysema at onset ≤45 years or without recognized risk factors, spontaneous pneumothorax, cervical artery dissection, liver biopsies showing periodic acid-Schiff positive inclusions, unexplained and isolated elevated transaminases, antineutrophil cytoplasmic antibodies, or low

<table>
<thead>
<tr>
<th>Authors</th>
<th>Detection strategy</th>
<th>Number of patients</th>
<th>Prevalence of specific AAT phenotype (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matzen et al.26</td>
<td>Case-finding (individuals with abnormal PFTs)</td>
<td>225 (US)</td>
<td>0</td>
</tr>
<tr>
<td>Lieberman et al.11</td>
<td>Case-finding (patients with advanced COPD admitted for carotid body surgery)</td>
<td>965 (US)</td>
<td>1.9, 0.3, 7.7, 0.3, 10.1</td>
</tr>
<tr>
<td>Luisetti et al.25, Ferrarotti et al.33</td>
<td>Case-finding (missing or reduced α1 globulin band, early-onset emphysema, familial cluster, first-degree relative of subjects with ascertained AATD or MZ heterozygosity)</td>
<td>2127 (Italy)</td>
<td>7.3, 1.9, 17.9, 0.05, 6.6, Null, Null, 0.4, Z null 0.2, Rare variants 0.2</td>
</tr>
<tr>
<td>Wencker et al.27</td>
<td>Targeted detection (patients with COPD, emphysema, asthma, or bronchiectasis)</td>
<td>1060 (Germany)</td>
<td>0, 0.2, 3.7, 0.09, 3.4, PI*M Null 0.09</td>
</tr>
<tr>
<td>Brantly et al.22</td>
<td>Case-finding (targeted detection in COPD with education program and free testing)</td>
<td>969 (Florida)</td>
<td>3.2, 0.4, 11</td>
</tr>
<tr>
<td>de la Roza et al.24</td>
<td>Case-finding (patients with COPD)</td>
<td>2137 (Spain)</td>
<td>0.37, 0.14, 0.14</td>
</tr>
<tr>
<td>Corda et al.23</td>
<td>Case-finding (emphysema without risk factors or of early-onset, spontaneous pneumothorax, cervical artery dissection, PAS positive bodies in liver, isolated transaminase elevation, ANCA positive, or low alpha-1 proteins on protein electrophoresis)</td>
<td>285 (Italy)</td>
<td>12, 8, 62, 14, PI<em>ZI 0.35, PI</em>ZM_malton 0.35, PI*MW_malton 2.1</td>
</tr>
<tr>
<td>Bals et al.21</td>
<td>Case-finding linked to an AATD awareness program</td>
<td>2696 (Germany)</td>
<td>9.9, 2.0, 18.1, 3.6, Rare phenotype 0.5</td>
</tr>
<tr>
<td>Rahaghi et al.34</td>
<td>Case-finding</td>
<td>29 (US)</td>
<td>0, 1</td>
</tr>
</tbody>
</table>

PAS, periodic acid-Schiff; ANCA, antineutrophil cytoplasmic antibodies.

Table 2: Results of studies undertaken to detect individuals with AATD.
alpha-1 globulin on serum protein electrophoresis. Overall, of 285 specimens collected over 9 years, 211 (74%) alpha-1 antitrypsin deficient specimens were identified as follows: PI*ZZ = 12% (N = 26), PI*SZ = 8% (N = 17), PI*ZI = 0.35% (N = 1), PI*ZM, null = 0.35% (N = 1), PI*MZ = 62% (N = 131), PI*MS = 14% (N = 29), and PI*M,M null = 2.1% (N = 6).23

Wencker et al. conducted a targeted-detection study for AATD in 7 German physicians’ offices – 3 pulmonologists and 4 general practitioners. Between March and June 1999, patients with COPD, asthma, or bronchiectasis were offered AATD testing using dried blood spot samples for immunoassay and isoelectric focusing. Of 1060 evaluable samples, 77% were submitted by pulmonologists. None of the 1060 samples was PI*ZZ, 3 (0.2%) were PI*SZ, 1 (0.09%) was PI*M null, 1 (0.09%) was PI*SS, 39 (3.7%) were PI*MZ and 36 (3.4%) were PI*MS.27

Luisetti et al. reported the results of an Italian program in which dried blood spot alpha-1 antitrypsin tests were distributed to hospitals and clinics between 1993 and 1998. Testing was suggested for individuals with low alpha-1 antitrypsin protein amounts on serum protein electrophoresis specimens, individuals known to have serum alpha-1 antitrypsin levels <80 mg/dl, those with early-onset emphysema, a history of familial COPD, or first-degree relatives of those known to have AATD, including PI*MZ. Of 1841 samples, a total of 151 (18%) were found to have AATD. With both phases taken together, the number of 1841 samples, a total of 151 (18%) were found to have AATD. With both phases taken together, the number of samples was PI*ZZ, 3 (0.2%) were PI*SZ, 1 (0.09%) was PI*M null, 1 (0.09%) was PI*SS, 39 (3.7%) were PI*MZ and 36 (3.4%) were PI*MS.27

Of the targeted-alpha-1 antitrypsin deficiency detection programs shown in Table 2, the highest detection rates are found in those that include an awareness campaign.21,22 or in those that broadly target specific clinical features of alpha-1 antitrypsin deficiency.23,25,29 On the other hand, several studies which tested a relatively small number of individuals (e.g., <200) identified no AATD individuals.26,34

In an analysis of the “number needed to test” in order to identify a single individual with severe deficiency of alpha-1 antitrypsin, Rahaghi et al. estimated that approximately 150 targeted patients would need to be tested in order to have a 95% confidence of detecting a single individual with severe AATD in a population in which the prevalence of severe AATD among COPD patients is 2%.34

As another strategy to enhance clinicians’ awareness of and testing for AATD, Rahaghi et al. appended physician alerts suggesting testing for AATD to the pulmonary function test reports of patients found to have fixed airflow obstruction. During the “physician alert intervention period,” the rate of testing for AATD was higher than during the control period (prior to issuing the physician alerts, 13% vs. 6%), though the absolute rate of testing remained low and no patient with severe AATD was detected during the study.34

Enthusiasm to encourage clinicians to test all symptomatic adults with fixed airflow obstruction has prompted a study that is currently being launched in which an electronic medical record prompt will go the clinician who has ordered a pulmonary function test whenever the patient’s pulmonary function test result indicates fixed airflow obstruction. Finally, the Alpha-1 Foundation has launched a study, also currently underway, in which patients whose pulmonary function tests show fixed airflow obstruction are approached immediately in the pulmonary function laboratory and offered the opportunity to be tested for AATD. Whether these strategies of electronic prompts or directly approaching patients for AATD testing will enhance detection must await the results of these planned or recently initiated studies.

Other strategies to encourage testing for AATD include developing tests that are easy and that are acceptable to patients. Such tests are available and include alpha-1 antitrypsin genotyping from mouthwash specimens,35 testing of dried blood spots,27 and home testing with confidential results reporting (the Alpha-1 Coded Testing [ACT] Trial).36

In considering the potential limitations of targeted-detection programs, one shortcoming is that targeting symptomatic individuals overlooks the possibility of detecting asymptomatic and/or clinically unaffected individuals with severe deficiency of alpha-1 antitrypsin. The magnitude of such a bias has been suggested by studies which estimate the frequency with which individuals with severe AATD actually develop clinical signs or symptoms. For example, Tobin et al. attempted to lessen the selection bias of studying individuals attending a chest clinic by assessing the risk of developing emphysema in PI*ZZ siblings of index cases.13 In this study, emphysema was radiographically confirmed in 90% of PI*ZZ smokers compared to 65% of PI*ZZ non-smokers.13 Similarly, data from the Swedish National Registry, in which only 29% of the participants were identified on the basis of lung disease, showed that in adult PI*ZZ homozygotes, 29% of never-smokers and 10% of ever-smokers were healthy.37 Post-mortem series from Sweden,37 and computed tomographic studies38 also indicated that approximately 14–20% of PI*Z homozygotes escaped developing emphysema. de la Roza et al. have estimated that 35–60% of PI*ZZ develop COPD.34 Finally, Silverman et al. reported that only 10 of 30 PI*ZZ individuals, who were not diagnosed because of existing lung disease, had FEV1 < 65%.39 Taken together, the results of these studies support the notion that targeted detection, which has been shown to be cost-effective by the conventional criterion of <$50,000 per quality-adjusted life-year,40 may underestimate the prevalence of individuals with AATD by virtue of overlooking those who are free of clinical manifestations of AATD. Population-based studies avoid this potential source of bias but are, of course, challenging to perform on a large scale.

Summary

Alpha-1 antitrypsin deficiency remains under-recognized despite increased attention to the issue through the publication of management guidelines,1 awareness campaigns by various patient advocacy organizations, and a growing number of recent publications.41 A diagnosis of AATD may have important implications, including testing of family members, genetic counseling, smoking avoidance,
avoidance of high-risk occupations, and consideration of augmentation therapy. Enthusiasm to enhance detection has prompted a variety of studies to identify affected individuals, including direct population screening, targeted detection of individuals regionally or nationally, and strategies to enhance clinician’s suspicion and testing for alpha-1 antitrypsin deficiency. Compared to population-based studies, which are difficult to perform on a large scale, targeted-detection programs have a much higher rate of detection of AATD, are easier to perform, and are more cost-effective, though they may miss asymptomatic individuals. Characteristics of the studies that have the highest detection rates include those that provide confidential and easy to perform testing, and broadly target specific clinical features of alpha-1 antitrypsin deficiency combined with an awareness campaign.\textsuperscript{21,22}

Conflict of interest

Dr. Aboussouan has no conflicts of interest to disclose. Dr. Stoller has indicated that he has been a consultant for Talecris and Baxter corporations.

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