

# Trends in the Diagnosis of Symptomatic Patients With $\alpha_1$ -Antitrypsin Deficiency Between 1968 and 2003\*

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**Background:**  $\alpha_1$ -Antitrypsin deficiency (AATD) is usually underrecognized, with only 5% of cases being diagnosed in the estimated 100,000 affected individuals in the United States. To support current guidelines recommending AATD testing of all individuals with COPD, we analyzed the diagnostic experience of a large cohort of symptomatic patients with AATD.

**Methods:** A total of 1,020 members of AlphaNet, a not-for-profit health management company devoted to patients with AATD, provided information regarding their AATD diagnostic experience as part of a larger survey-based outcome study.

**Results:** The average age at diagnosis was  $45.5 \pm 9.5$  years, and the average interval between the onset of symptoms and diagnosis was  $8.3 \pm 6.9$  years ( $\pm$  SD); 30.8% were diagnosed in patients > 50 years old. Two thirds of the diagnoses were made by the first or second physician, and 20% by the fourth or more physicians. From 1968 to 2003, there was a steady increase in age at diagnosis ( $p < 0.05$ ), the number of physicians required for diagnosis ( $p > 0.05$ ), and years with symptoms before diagnosis ( $p > 0.05$ ), while the proportion of cases diagnosed by the first or second physician decreased ( $p < 0.001$ ). Individuals with a diagnosis at < 35 years of age saw fewer physicians than other age groups ( $p < 0.05$ ), and show a tendency toward a shorter diagnostic interval over time ( $p > 0.05$ ). Diagnoses were made in men earlier than in women ( $p < 0.05$ ), and the proportion of individuals in whom AATD was detected because of asthma or COPD has increased ( $p < 0.05$ ).

**Conclusion:** There has not been a significant improvement in earlier disease diagnosis between 1968 and 2003. There has been improved AATD detection in older individuals. The diagnostic delay is still significant, and efforts should be directed to increase early AATD detection by health-care providers and patients. (CHEST 2005; 128:1179–1186)

**Key words:**  $\alpha_1$ -antitrypsin deficiency; detection; diagnosis; survey

**Abbreviations:** AAT =  $\alpha_1$ -antitrypsin; AATD =  $\alpha_1$ -antitrypsin deficiency; ASPIRE = AlphaNet System for Patient Information and Research Endeavors; ATS = American Thoracic Society; ERS = European Respiratory Society

**A**lpha1-antitrypsin (AAT) is a serine protease inhibitor synthesized primarily by hepatocytes that reaches the alveoli by passive diffusion from the circulation and protects the alveolar matrix from proteolytic attack, particularly by neutrophil

elastase.<sup>1</sup> Several mutations have been described that can lead to abnormal AAT variants. The most important deficiency variant of AAT is the Z mutation (Glu342Lys, known as PiZ). This mutation alters the tertiary structure of the protein, affecting its ability to bind to elastase and promoting the formation of polymers, which accumulate within the endoplasmic reticulum of hepatocytes.<sup>2</sup> The accumulation of protein in these cells causes liver damage in some affected individuals (by mechanisms that are still unclear) and is associated with a secretory defect resulting in low serum AAT levels. The low serum level then leaves the lung tissue exposed to uncontrolled proteolytic attacks from neutrophil elastase, culminating in alveolar destruction and panacinar emphysema, in particular during exposure to cigarette smoke, environmental irritants, or infections.

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Genetic epidemiology studies<sup>3,4</sup> indicate that AAT deficiency (AATD) may be one of the most common serious hereditary disorders in the world. Data pooled from studies of 58 countries (total population 4.4 billion including several nonwhite populations), indicate that worldwide there are at least 116 million carriers of abnormal alleles and approximately 3.4 million with severe deficiency allele combinations (such as PiSS, PiSZ, PiZZ, PiZNull and PiNullNull).<sup>3</sup> In the United States, on the basis of a population of about 260 million, the estimated prevalence is from 80,000 to 100,000 individuals for both symptomatic and asymptomatic individuals,<sup>4</sup> a number comparable with the prevalence in Europe.<sup>5</sup>

It is estimated that AAT deficiency has been diagnosed in only 5,000 individuals in the United States. Therefore, it appears the disease is either undiagnosed or not associated with disease in approximately 95% of affected individuals. The absolute prevalence of AATD-related pulmonary disease is unknown, but targeted-detection testing in symptomatic populations has led to an estimate of its prevalence in symptomatic individuals. For example, in one study,<sup>6</sup> the prevalence of PiZZ individuals among 965 patients with diagnosed COPD was 1.9%. The general estimate is that 1 to 3% of the 10 million individuals with COPD in the United States have AATD (at least 100,000 individuals), and this has led to recommendations by the American Thoracic Society (ATS) and European Respiratory Society (ERS) to test all individuals with COPD or incompletely reversible asthma.<sup>4</sup>

Despite these recommendations, it appears that this disease is still largely undetected or misdiagnosed, especially in its early stages. A patient survey performed in the mid-1990s suggested that at that time the diagnosis was made an average of 7 years after symptoms first appeared, with almost half of individuals receiving a diagnosis after being seen by at least three physicians.<sup>7</sup> The postulated advantages of an early diagnosis of AATD include counseling for healthier lifestyles (specially smoking cessation), institution of preventive measures, and institution of specific augmentation therapy at earlier stages of lung disease (observational studies<sup>4,8</sup> suggest that augmentation therapy may potentially enhance survival and decrease the progression of pulmonary disease). Early detection of index cases may also facilitate genetic counseling and lead to detection of affected relatives before the development of lung disease.

AlphaNet is a non-for-profit health management company that coordinates services for individuals with AATD. Its activities include providing follow-up and disease management services for its 2,700 mem-

bers, most of whom are receiving augmentation therapy. As part of their incentive to improve care, a study evaluating the health impact of their patient-oriented disease management program has been launched. The baseline information collected for this study included several questions regarding the diagnosis of AATD. In view of the current recommendations to test all symptomatic individuals at risk for AATD and the increasing efforts by organizations such as the Alpha-1 Foundation and the Alpha-1 Association to improve awareness of the disease among health-care providers and patients, we thought it important to analyze the diagnostic experience of this cohort of symptomatic patients over the past 35 years. This group represents approximately a third of all symptomatic patients with AATD receiving augmentation therapy in the United States.

## MATERIALS AND METHODS

### *Subjects*

AlphaNet members are individuals with AATD who provide written consent to be followed up by AlphaNet and its regionally based disease management coordinators. Most members have lung disease and are receiving augmentation therapy at the time of enrollment in the AlphaNet program. All AlphaNet members are monitored by telephone on a monthly basis by 1 of 23 regional coordinators, all of whom are AATD patients who have received formal training in disease management. The AlphaNet coordinators provide customer service and supply ordering for their patients receiving augmentation therapy and are backed up by a full-time medical team devoted to this patient population. In addition, the AlphaNet coordinators administer questionnaires for a variety of research projects that AlphaNet members may individually consent to participate in.

For this current study, all 2,700 AlphaNet members were invited to participate in the AlphaNet Outcome Study. Coordinators were trained by the investigators to participate in the enrollment process and perform follow-up surveys for the study. AlphaNet members who expressed interest in learning about this study received information by mail and after an initial positive verbal response were called by their coordinators to review the consent form. Individuals who agreed to participate mailed their signed informed consent forms directly to the investigators for review and official enrollment in the study. The Institutional Review Board at the University of Miami approved this enrollment process. A total of 1,020 individuals provided signed informed consent and completed the baseline questionnaire.

### *Collection and Storage of Data*

Enrollment and baseline data collection were obtained by telephone interviews between February and July 2003. Experienced surveyors (Harbaugh Associates; Exeter, NH) performed the baseline questionnaire, which produced the data analyzed in this report. All survey results were by telephonic conversation and were directly entered at the time of collection in a validated, proprietary database (the AlphaNet System

for Patient Information and Research Endeavors [ASPIRE]). ASPIRE and its data entry system are compliant with all US medical research confidentiality requirements in place at the time of the study. The investigators retrieved the data directly from ASPIRE for analysis.

#### Demographic and Clinical Data

The initial baseline survey was a comprehensive questionnaire with several questions devoted to the diagnosis of AATD, including age at diagnosis, year of diagnosis, years with symptoms before diagnosis, the number of physicians seen before correct diagnosis, as well as general demographic, clinical, and epidemiologic data. More complete clinical, demographic, and quality-of-life data will be the subject of a subsequent report.

#### Statistical Analysis

Data were analyzed using statistical software (SAS 9.13 for Windows; SAS Institute: Cary, NC; and Statistix Version 7.1; Analytical Software; Tallahassee, FL). A Kolmogorov-Smirnov test was used to examine the normal distribution of quantitative data. Quantitative data were expressed as mean  $\pm$  SD. Since not all participants answered all the questions, percentages for specific items were adjusted according to the number of answers available.  $\chi^2$  test was used to compare proportions. Differences in means between groups were compared with Student *t* test and analysis of variance. Significance was accepted at the 5% level.

## RESULTS

A total of 1,020 individuals with AATD who were receiving ( $n = 958$ ) or had previously received ( $n = 62$ ) augmentation therapy for AATD-related lung disease answered questions regarding their diagnosis. The group included patients who had undergone lung ( $n = 33$ ) or liver ( $n = 1$ ) transplantation. Even though 15% of our subjects received a diagnosis after a diagnosis was made in a relative, they all reported symptomatic lung disease at the time of diagnosis: 76.8% had a physician diagnosis of COPD or emphysema, and 43.3% reported a diagnosis of asthma with (39.1%) or without (4.1%) COPD. The individuals in this cohort reported a diagnosis made between 1968 and 2003. Seven patients did not provide the year of AATD diagnosis, 25 did not provide the number of physicians seen before a diagnosis, and 18 did not provide the number of years with pulmonary symptoms before a diagnosis. The average age of the respondents was  $54.2 \pm 9.5$  years; 52% were male, and the average time since the diagnosis of AATD was  $8.8 \pm 6.3$  years.

#### Age at Diagnosis of AATD

The average age at diagnosis for the whole group was  $45.5 \pm 9.5$  years, and the average interval between the onset of pulmonary symptoms and diagnosis was  $8.3 \pm 6.9$  years ( $17.0 \pm 8.7$  years

from the onset of symptoms to study entry). Figure 1, *top*, A shows the distribution of age at diagnosis. Most diagnoses were made in patients from 40 to 49 years of age, but 30.8% were made in patients  $> 50$  years old. When individuals with diagnoses in recent years (2000 and beyond,  $n = 200$ ) were analyzed separately, the age-distribution curve shifted to the right, indicating that in recent years the population with an AATD diagnosis was significantly older ( $p < 0.05$ , Fig 1, *bottom*, B). A comparison of the average age at diagnosis over different time periods confirmed that the average age at diagnosis has increased steadily over time (Fig 2, *bottom*, C). For example, the average age at diagnosis was 40.8 years (95% confidence interval, 39.6 to 42 years) before 1990, and 48.5 years (95% confidence interval, 47.2 to 49.8 years) after year 2000 ( $p < 0.05$ ).

#### Number of Physicians To Diagnose AATD

The average number of physicians seen by the cohort before AATD was correctly diagnosed was  $2.7 \pm 2.4$ . Overall, one third (33.8%) reported a correct diagnosis by the first physician, and another third (31.8%) by the second physician, while one fifth had to see four or more physicians before a diagnosis, 10.8% received a diagnosis by the fourth or fifth physician, and another 9% had to see six or more physicians before a correct diagnosis was made. Paralleling the observed increase in age at diagnosis in recent years, the average number of physicians seen before AATD diagnosis also showed a trend toward increasing numbers, but it did not reach statistical significance (Fig 2, *top*, A). However, subgroup analysis showed that the percentage of subjects with a correct diagnosis by either the first or second physician has been decreasing in recent years, from 78.2% for patients with a diagnosis before 1990 ( $n = 254$ ), to 67.6% for individuals with a diagnosis from 1990 to 1994 ( $n = 207$ ), 61% for individuals with a diagnosis from 1995 to 1999 ( $n = 352$ ), and 57.6% for individuals with a diagnosis after 1999 ( $n = 200$ ) [ $p < 0.001$ ]. Figure 3 shows this difference when comparing individuals with a diagnosis after 1999 to individuals with a diagnosis in 1999 and before.

In order to analyze the influence of age on the number of physicians needed to diagnose AATD, the cohort was divided by age groups: diagnosis before age 35 years ( $n = 103$ ), diagnosis from 35 to 44 years ( $n = 398$ ), diagnosis from 45 to 54 years ( $n = 330$ ), and diagnosis at  $\geq 55$  years ( $n = 181$ ). Individuals with a diagnosis of AATD before age 35 years had to see significantly fewer physicians for a diagnosis when compared with all other age groups

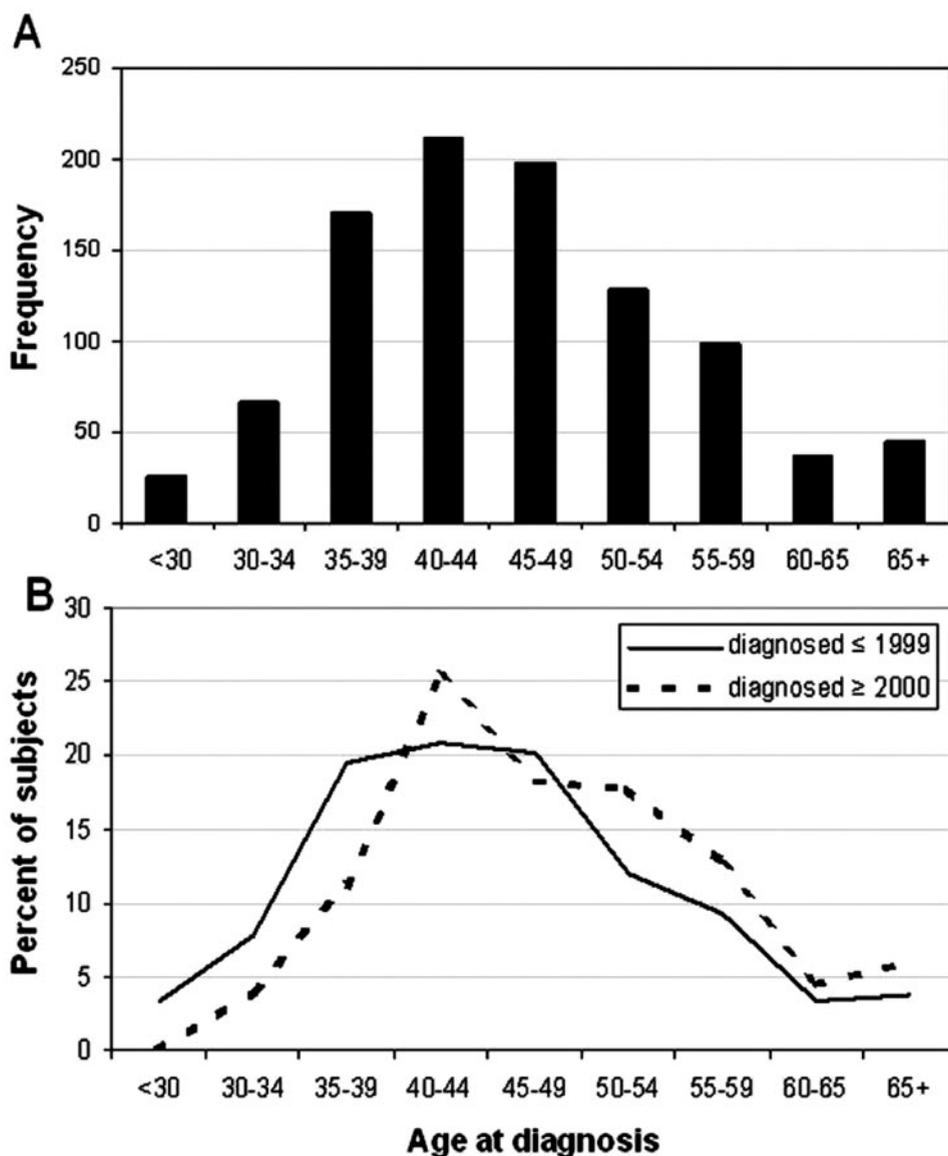


FIGURE 1. Distribution of ages at diagnosis in patients with AATD. *Top, A:* Frequency distribution of ages at diagnosis, showing the majority of participants with a diagnosis between the ages of 40 and 50 years. *Bottom, B:* Comparison of age at diagnosis distribution curves for subjects with a diagnosis after 2000 (n = 200) or before 2000 (n = 813) [p < 0.05].

( $2.1 \pm 1.8$  for the group < 35 years old vs  $2.7 \pm 2.6$ ,  $2.7 \pm 2.1$ , and  $2.9 \pm 2.6$  for the other groups, respectively;  $p = 0.01$ ). There was no statistical difference observed between the other age groups. As expected, the percentage of individuals with a diagnosis made by either the first or second physician decreased as the individual's age at diagnosis increased, but it did not reach statistical significance either (72.9%, 69.9%, 63.8%, and 59.6% for the same age groups, respectively;  $p = 0.1$ ). Figure 4 shows the diagnostic experience of these four age groups over time. Figure 4, *top*, A shows that within each one of the age groups, in

recent years there has not been a significant reduction in the total number of physicians seen before AATD was correctly diagnosed.

#### Years With Symptoms Before AATD Diagnosis

In accordance with the above findings, the interval between the onset of pulmonary symptoms and the time when the disease was correctly diagnosed has trended to increase in recent years. The average number of years with symptoms before AATD diagnosis was  $6.5 \pm 5.1$  years for individuals with a diagnosis before 1990,  $7.1 \pm 4.6$

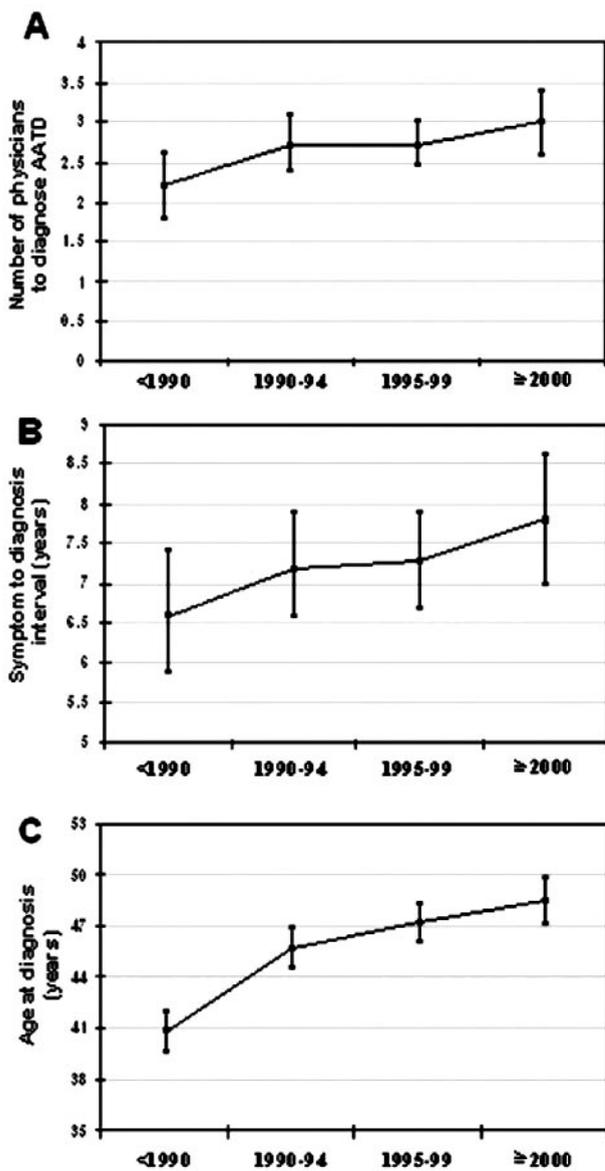


FIGURE 2. Diagnostic experience of subjects with AATD by year of diagnosis. *Top, A*: The average number of physicians seen before correct diagnosis trends to increase over time ( $p > 0.05$ ). *Center, B*: The average number of years with symptoms before diagnosis trends to increase over time ( $p > 0.05$ ). *Bottom, C*: The average age at diagnosis significantly increased over time ( $p < 0.05$  between diagnosis  $\leq 1990$  and all other year groups, and between the 1990–1994 year group and the group with a diagnosis after 2000).

years for individual with a diagnosis from 1990 to 1994,  $7.2 \pm 5.1$  years for individuals with a diagnosis from 1995 to 1999, and  $7.8 \pm 5.5$  years for individuals with a diagnosis in 2000 and beyond ( $p = 0.2$ , Fig 2, center, B).

When analyzed by age groups, it is not surprising to note that younger individuals spend less time symptomatic before a correct diagnosis is made. For individuals with a diagnosis made be-

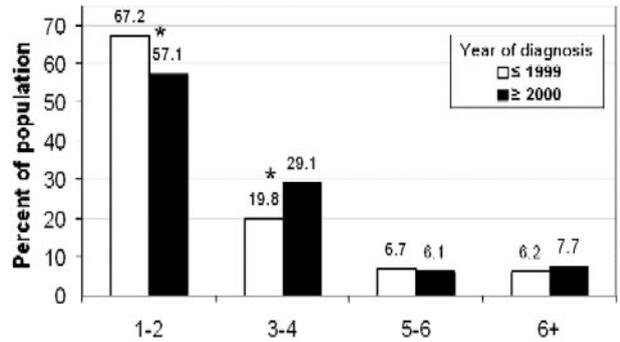


FIGURE 3. The number of physicians seen before an accurate diagnosis of AATD by year of diagnosis. The proportion of subjects with a diagnosis by the first or second physician has significantly decreased in recent years, while the proportion of subjects needing to see three to four physicians for a correct diagnosis has increased.  $*p < 0.05$ .

fore the age of 35 years, the mean interval with symptoms was  $5.5 \pm 4.1$  years; for individuals with a diagnosis made at 35 to 44 years of age, the mean interval with symptoms was  $6.0 \pm 4.1$  years; for individuals with a diagnosis made at 45 to 54 years of age, the mean interval with symptoms was  $7.7 \pm 5.0$  years; and for individuals with a diagnosis made at  $\geq 55$  years, the mean interval with symptoms was  $9.2 \pm 6.5$  years ( $p < 0.001$ ). There was a difference between all groups except for the groups with a diagnosis from 45 to 54 years, and  $\geq 55$  years. An analysis of the diagnostic experience of these four age groups over time shows that within each age group, in recent years there has not been a significant reduction in the total number of years with symptoms before the diagnosis of AATD, although there is a trend to decrease in the group with a diagnosis at age  $< 35$  years (Fig 4, bottom, B).

#### Effect of Gender in the Diagnosis of AATD

The symptom interval before diagnosis was significantly lower in men than in women for the entire cohort ( $6.8 \pm 4.8$  years vs  $7.6 \pm 5.4$  years, respectively;  $p = 0.02$ ). There were no significant differences in the age at diagnosis or the number of physicians seen between men and women ( $45 \pm 9.3$  years vs  $46 \pm 9.7$  years and  $2.5 \pm 2.3$  physicians vs  $2.7 \pm 2.5$  physicians, respectively). There was no significant difference in the proportion of women or men with a diagnosis of AATD before or after 2000. When each gender was analyzed separately, the only difference between individuals with a diagnosis before or after 2000 was in age:  $45.1 \pm 9.5$  years vs  $49 \pm 9.8$  years for women ( $p = 0.0003$ ), and  $44.9 \pm 9.3$  years vs  $47.9 \pm 9.1$  years for men ( $p = 0.003$ ).

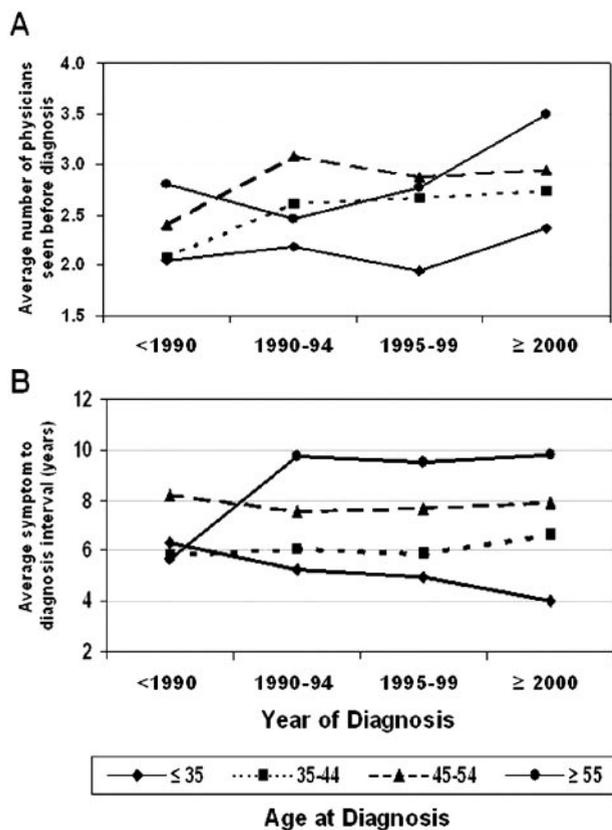


FIGURE 4. The diagnostic experience of subjects with AATD by age groups. *Top, A:* The number of physicians required for correct diagnosis. Within each age group, there was no statistically significant difference in the number of physicians seen before a correct diagnosis over time. Younger individuals see significantly fewer physicians before diagnosis compared with all other age groups through all years studied ( $p < 0.05$ ). *Bottom, B:* Years from symptoms to diagnosis of AATD. There is no decrease in the diagnostic delay across the years studied for any age group. The diagnostic delay is significantly different between all age groups except for the two younger groups.

#### Factors Affecting the Diagnosis of AATD

Table 1 shows the reasons why AATD was suspected in the surveyed population. The three most common reasons were unexplained dyspnea, a prior clinical diagnosis of COPD (either emphysema or chronic bronchitis), and having a relative with a diagnosis of AATD. A prior diagnosis of asthma or COPD increased after 2000 ( $p < 0.005$ ). There were seven patients who reported bronchiectasis as their main pulmonary diagnosis (included in the “other” group in Table 1) and, in general, they had a delayed diagnostic experience (mean age at diagnosis,  $49 \pm 9$  years; symptom interval,  $12.2 \pm 9$  years; and average number of physicians seen,  $5.8 \pm 4$ ).

#### DISCUSSION

Efforts to raise awareness of AATD have been advocated by several organizations. In 1996, the

World Health Organization issued statements recommending screening in all symptomatic individuals with obstructive lung diseases,<sup>9</sup> and organizations like the Alpha-1 Association and the Alpha-1 Foundation have been trying to increase awareness of the disease by emphasizing how many individuals are misdiagnosed by health care providers. These efforts, along with the development of easier screening techniques such as the dried blood spot method<sup>10</sup> have likely made an impact in the detection of AATD in recent years. The data reported in the present article reflect AATD detection trends in the United States over the past 4 decades, and support a statement by the ATS and ERS that recommends AATD screening of all symptomatic patients with COPD or adults with asthma who have airflow obstruction that is incompletely reversible after aggressive treatment with bronchodilators.<sup>4</sup>

Even though two thirds of individuals in our cohort reported a correct diagnosis by the first or second physician, a large fraction had an important delay in their diagnosis, with several having to see more than six physicians before a correct diagnosis was made. The only previous report<sup>7</sup> addressing the diagnostic experience in AATD is a 1994 survey-based study in 304 individuals with severe AATD. That study<sup>7</sup> found that 43% of individuals required three or more physicians to diagnose the disease after an average of  $7.2 \pm 8.3$  years from the onset of respiratory symptoms. In comparison and considering that our survey did not include subjects who were asymptomatic at diagnosis, we describe a considerably higher percentage of individuals with a correct diagnosis by the first physician (33.8% vs 25.1%), fewer individuals with a diagnosis by the third or fourth physicians (10.8% vs 13.6%), and fewer individuals needing six or more physicians for a correct diagnosis (9% vs 12.5%). In contrast, we observed a higher mean age at diagnosis and a longer symptom interval; which, along with the number of physicians required for a correct diagnosis of the disease, show a persistent tendency to increase over the years we studied. These differences are likely because cohorts that include asymptomatic individuals with diagnoses made through a variety of mechanisms, including family testing and screening, would be expected to give a spuriously shorter delay in diagnosis. We consider our symptomatic cohort to be a more relevant group to evaluate. In recent years, efforts to increase AATD awareness have led to increased detection of older individuals with apparent cigarette smoke-induced COPD who were not previously being tested for AATD. Since the data analyzed in this report were collected before the ATS/ERS document<sup>4</sup> on standards for

**Table 1—Analysis of Factors Leading to Diagnosis of AATD by Year of Diagnosis\***

Variables	All Patients	Diagnosis $\leq$ 1999	Diagnosis $\geq$ 2000	p Value
Reason leading to AATD diagnosis				
Dyspnea	294 (30.0)	235 (30.1)	59 (29.4)	0.83
COPD	233 (23.8)	179 (23.0)	54 (26.9)	< 0.0001
Relative with AATD	147 (15.0)	124 (15.9)	23 (11.4)	0.11
Asthma	108 (11.0)	75 (9.6)	33 (16.4)	0.006
Frequent respiratory infections	58 (5.9)	50 (6.4)	8 (4.0)	0.19
Incidentally†	41 (4.2)	37 (4.7)	4 (2.0)	0.42
Liver disease	44 (4.5)	37 (4.7)	7 (3.5)	0.44
Other	56 (5.7)	43 (5.5)	13 (6.5)	0.60
Tobacco exposure	809 (82.5)	641 (82.2)	168 (83.6)	0.64
Report occupational exposure to dust, fumes, or smoke	201 (20.5)	161 (20.6)	40 (19.9)	0.82

\*Data are presented as No. (%).

†Cases in which diagnosis was suspected from routine physical examination, work-related routine spirometry, or during work-up for unrelated disease.

the diagnosis and management of AATD individuals, the impact of their screening recommendations is yet to be seen.

Even though late recognition of AATD has increased, analysis of the diagnostic experience by individual age groups suggests that in recent years there has not been an overall improvement in early disease detection. For example, our data suggest that an individual with a diagnosis between the ages of 35 and 44 years in 1990 requires the same number of physicians and has a similar number of symptomatic years as an individual of the same age group who received a diagnosis in 2001. These findings apply for all but one of the age groups analyzed. The average percentage of individuals diagnosed by the first or second physician has also been decreasing over time, but this has also not improved over the years when corrected by age at diagnosis.

An analysis of symptoms data in the National Institutes of Health Registry of AATD patients suggested that the disease presents with common respiratory symptoms such as nonspecific dyspnea, bronchitis, asthma, or non-AATD emphysema.<sup>11</sup> In our cohort, the proportion of subjects with a diagnosis because of COPD or asthma has significantly increased since 2000. It is important to recognize that individuals with AATD have a high prevalence of asthma-like features,<sup>12,13</sup> and that a bronchodilator response is associated with a more rapid FEV<sub>1</sub> decline.<sup>8</sup> Our data show that men experience a shorter diagnostic delay than women, presumably due to the gender bias that physicians have in the diagnosis of COPD.<sup>14</sup>

This is a survey-based report and therefore is subjected to recall bias, especially for events that occurred in the remote past. However, the cohort had similar responses to other large cohorts of AATD

such as the National Institutes of Health Registry<sup>11</sup> or the  $\alpha_1$  Research Registry.<sup>15</sup> There is also the possibility of participation bias, *ie*, subjects who know more about their disease and are more motivated to help others with similar conditions are more likely to participate. The motivation to participate might decrease a potential recall bias, but their diagnostic experience is not likely to be significantly different from subjects who decline to participate. Finally, there is the possibility of survivor bias: a larger proportion of individuals with a diagnosis at earlier time points may have died prior to the survey, compared with individuals with a more recently diagnosis. There are no data suggesting that individuals who die soon after the diagnosis of AATD have a different diagnostic experience than those who have a longer survival. However, if we assume that individuals with a shortened survival are symptomatic earlier in life and have more rapid disease progression, we would expect to see a shorter diagnostic delay in the youngest age group at the most recent time points. While there was a trend toward this in the youngest age group, this trend was not statistically significant.

In conclusion, analysis of the diagnostic experience of our cohort of symptomatic patients suggests that while the diagnosis of AATD has increased in older patients with advanced disease in recent years, early detection has not improved. The diagnostic delay is still present, and efforts to increase AATD awareness may have to be directed to emphasize early diagnosis among health-care providers and patients.

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