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Alpha$_1$-antitrypsin deficiency – Diagnostic testing and disease awareness in Germany and Italy☆

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Summary
Background: Alpha$_1$-antitrypsin (AAT) deficiency, although largely under-diagnosed, is the underlying cause of approximately 1% of COPD cases. Lack of awareness leads to long delays in diagnostic testing. Subsequently, lifestyle and treatment choices with potentially positive effects on prognosis may be postponed.
Methods: Data on the testing and diagnostic practices for AAT deficiency were derived from the University of Pavia, Italy, and the University of Marburg, Germany. In addition, a survey of physicians was undertaken to explore their awareness and attitudes toward AAT deficiency.
Results: In Pavia and Marburg, 125 and 729 patients, respectively, were identified with severe AAT deficiency between July 2006 and June 2011. The median time interval between the onset of symptoms and diagnosis was 6 years (interquartile range [IQR], 11; range, 0–40) and 7 years (IQR, 13; range, 0–73), respectively. Augmentation therapy was initiated almost immediately in Germany while treatment was delayed by 3 months in Italy (IQR, 5.25; range, 1–118). Survey data (Italy, $n = 181$; Germany, $n = 180$) revealed that pulmonologists had greater knowledge

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of AAT deficiency than internists and general practitioners, however, overall, only 18—25% of physicians tested all COPD patients. One-third of the respondents stated that they "sometimes" offered augmentation therapy to patients diagnosed with AAT deficiency.
Conclusions: Major obstacles to AAT deficiency testing are physicians' attitudes and lack of understanding of the condition. A greater adherence to the guidelines that recommend diagnostic testing of all COPD patients, coupled with simpler testing protocols, may decrease delays and positively impact patient outcomes.

Introduction

Alpha$_1$-antitrypsin (AAT) deficiency is a co-dominant hereditary disorder. This condition, which is characterized by low serum levels of alpha$_1$-proteinase inhibitor (alpha$_1$-PI), was first described in 1963.[1] Alpha$_1$-PI is a 52 kDa protein that is produced and secreted primarily in hepatocytes.[2] Although present in all body tissues, the primary physiologic role of alpha$_1$-PI is in the lungs, where it protects the alveoli from damage by proteolytic enzymes through the inhibition of neutrophil elastase.[3] On a clinical level, AAT deficiency is associated with an increased risk of developing chronic obstructive pulmonary disease (COPD), especially in smokers.[4] Less clinically important conditions that are associated with AAT deficiency include a greater risk of developing liver disease, cutaneous panniculitis, vasculitis, and Wegener's granulomatosis.[5—8]

Even though AAT deficiency has been classified as a rare disease, it is one of the most common hereditary disorders.[9—12] Worldwide, it has been estimated that 3.4 million individuals have an AAT genotype that leads to a deficiency of this protein.[13] Despite this, screening studies have established that less than 10% of affected individuals have been diagnosed.[14] Evidently, AAT deficiency is substantially under-recognized. Even among the individuals diagnosed, surveys have shown that the majority of these diagnoses are delayed for 5—7 years, during which period patients will typically consult several medical professionals.[15—17] Therefore, it can be assumed that, during this time delay before their diagnosis, many patients will have experienced a major decline in lung function.

The World Health Organization recommends testing of all COPD patients,[18] and the European Respiratory Society and American Thoracic Society Guidelines recommend the testing of all symptomatic adults with persistent airway obstruction.[4] Nevertheless, the discrepancy between the estimated number of individuals with the disorder from epidemiologic screening studies[9,10,12,13] and the confirmed numbers of diagnosed patients suggests that the recommendations are not followed. A number of reasons have been put forward to explain this, including poor awareness of the disorder and the methods for testing; differences in the interpretation of testing results; the multi-step approach that is required for final diagnosis; and a perception that existing treatments are inadequate.[19] While these reasons are plausible, there is a lack of data to support them.

Earlier diagnosis should enable patients to adapt their lifestyles accordingly, including giving up smoking to limit the progression of their lung damage.[20] In addition, it has been suggested that the decline in forced expiratory volume in 1 s and progression of emphysema development can be attenuated by interventions such as substitution therapy with alpha$_1$-PI.[21—23] It is therefore important to identify the major obstacles that prevent a more prompt diagnosis of AAT deficiency so that they can be overcome in order to optimize diagnostic procedures.

The aim of the present study was to explore potential reasons for the discrepancy between the expected and diagnosed number of patients and for the diagnostic delay. We surveyed physicians in Italy and Germany regarding their awareness and knowledge of AAT deficiency to explore their opinions and attitudes towards the disease and its diagnosis. We also present data on laboratory testing from two major European laboratories that have specialized in the identification of individuals with this disorder.

Methods

Study sites and participants

Descriptive data on the testing and diagnosis of AAT deficiency were derived from the experience of two reference laboratories in Europe working on national programs for the detection of AAT deficiency, namely, the University of Pavia, Italy, and the University of Marburg, Germany. These two national programs for AAT deficiency detection, as well as the diagnostic flow charts used by the two laboratories, have already been described in detail.[9,24] A description of the type of data that were collected is shown in the Supplementary Information.

Registry data were obtained from the national registries of patients with AAT deficiency that have been established in Germany[25] and Italy.[26,27] These organizations are members of the international network of registries from 21 countries, the Alpha One International Registry (AIR).[28] The criterion for inclusion in the registries is the presence of severe AAT deficiency, defined by alpha$_1$-PI plasma concentrations less than 0.8 g/L. In addition, the patients must be adults and carriers of PiZZ, PiSZ, or another deficient genotypic variant of the gene coding for alpha$_1$-PI.

All data from the laboratory analysis or from the registries were obtained in or refer to the period from July 1 2006 to June 30 2011.

Information collected from the online survey

In order to obtain information on the awareness and knowledge regarding AAT deficiency and, in particular, the

experience of physicians who are testing for the disorder, an online survey was conducted during September 2011. Physicians from Italy ($n = 181$) and Germany ($n = 180$) who had previously agreed to participate in market research studies were randomly invited to participate in the survey. Pulmonologists, internal medicine specialists, and general practice physicians from hospitals and physician offices answered 15 questions, and the survey took them approximately 10 min to complete. Participants were paid an honorarium for completing the survey.

Physicians participating in the survey were asked about the number of COPD patients they treat per month and their knowledge of AAT deficiency and other respiratory diseases. The survey also collected information on the number of tests for AAT deficiency performed each month, the preferred approach to testing, and the communication between the laboratory and the physician, as well as between the physician and the patient. Finally, the survey obtained information on the physicians' use of augmentation therapy to treat their patients. The survey data were analyzed by country, by physician specialty, and by hospital or office setting. The full list of questions is shown as Supplementary Information.

Survey data-handling and statistical analysis

Possible participant responses to the survey questions differed depending on the type of question. These were converted to a numerical scale, where "none at all"/"totally disagree" = 1, "a little"/"somewhat disagree" = 2, "average"/"somewhat agree" = 3, and "very much"/"totally agree" = 4.

Descriptive statistics were used to summarize the data collected from the laboratories and registries in Germany and Italy. Categorical variables were described by frequencies and percentages, and continuous variables were expressed as median, range, and interquartile range (IQR).

Results

Phenotyping and genotyping

Between July 1 2006 and June 30 2011, 962 patients from the University of Pavia, Italy and 9393 patients from the University of Marburg, Germany were tested for AAT deficiency (Fig. 1). Of those tested in Germany, 1102 (11.7%) had come from family screening programs and 1450 (15.4%) of tests reported AAT levels that had previously been determined by serum testing. A total of 729 patients were diagnosed with severe AAT deficiency (Fig. 2). Of those tested in Italy, 259 (26.9%) originated from family screening and 386 (40.1%) of tests reported AAT serum levels (Fig. 1). In this laboratory, 125 patients were diagnosed with severe AAT deficiency (Fig. 2).

Genotype data were collected from the patients with a positive diagnosis of severe AAT deficiency in both reference laboratories. In Germany, 72.2% of patients had the PiZZ genotype, with PiSZ being the second most common (17.1%). PiZ/Rare and PiSS were detected in 4.4% and 4.3% of the AAT-deficient patients, respectively (Fig. 2). The PiZZ genotype was found in 60% of patients from Italy, with

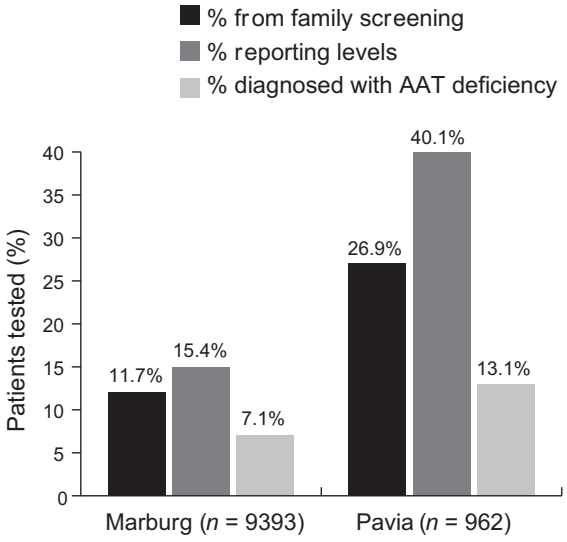

Figure 1 Components of total number of patients tested. The percentage of patient samples that originated from family screening programs, reported AAT levels, and were positively diagnosed in Marburg and Pavia.

PiZ/Rare as the second most common (18.4%), followed by PiSZ (11.2%). Rare genotypes that were identified in this laboratory included PiS/Rare and PiQ0/Q0 (both prevalent at a frequency of 3.2%).

Time intervals between onset of symptoms, testing, and reporting of results

Data collected from established national registries demonstrated that the median delay that index patients experience between showing symptoms of disease and receiving a diagnostic test is 7 years in Germany (IQR, 13; range, 0—73) and 6 years in Italy (IQR, 11; range, 0—40). In Germany, once a patient was tested for AAT deficiency, the median time interval before the result was communicated was 22 days (IQR, 20; range, 2—754), rising to 174 days (IQR, 302.5; range, 43—1146) when DNA sequencing was performed. In Italy, the median time interval from testing to results was 20 days (IQR, 13; range, 1—178) without sequencing, and 28 days (IQR, 23; range, 7—153) when DNA sequencing was performed.

Time lag between reporting of results and augmentation therapy

In Germany, there was little time delay between patients receiving their results and the start of their treatment (median, 0; IQR, 12; range, 0—408 months). In Italy, augmentation therapy was initiated after a median number of 3 months (IQR, 5.25; range, 1—118) after the results had been reported.

Results from the online survey

The composition of the respondents, by specialty, practice setting, and by number of COPD patients seen per month, is shown in Table 1.

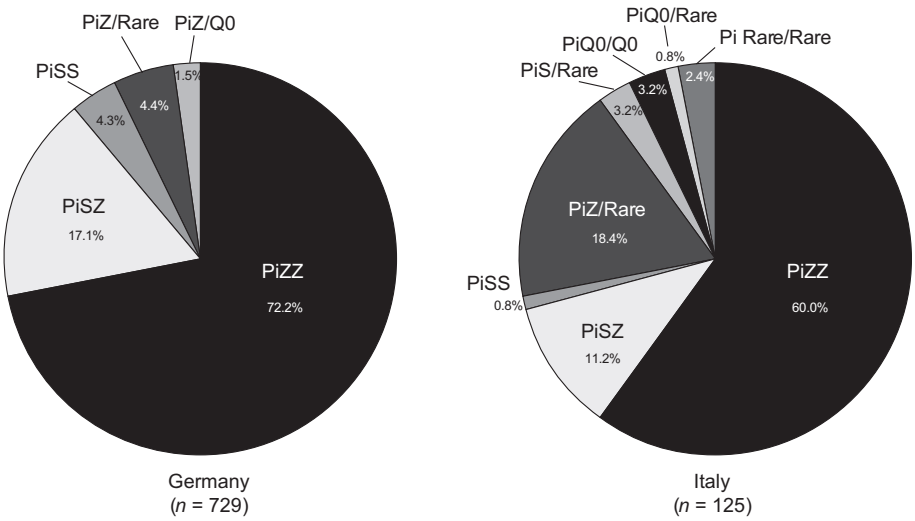

Figure 2 Genotypes of AAT-deficient individuals diagnosed from testing in Marburg, Germany, and Pavia, Italy.
The frequencies of the AAT deficiency genotypes identified in Germany and Italy are indicated. "Q0" denotes the "null" allele, in which the AAT gene is interrupted by a stop codon and no functional protein is produced. "Rare" includes all alleles other than M, S, and Z. Pi — proteinase inhibitor.

Knowledge regarding AAT deficiency

Compared with the four other respiratory diseases that respondents were asked about (COPD, sarcoidosis, cystic fibrosis, and idiopathic pulmonary fibrosis), the level of knowledge regarding AAT deficiency was lower in both Germany and Italy (2.8 and 2.5 for AAT deficiency vs 3.7 and 3.6 for COPD). In both countries, pulmonologists scored higher than internal medicine specialists (IMs) and general practitioners (GPs) (Germany: 3.5 vs 2.7 [IMs] and 2.4 [GPs]; Italy: 3.0 vs 2.4 [IMs] and 2.2 [GPs]). In addition, hospital-based physicians in both countries had a greater awareness of all of these respiratory conditions than did office-based physicians.

Physicians in Germany rated their personal perception of their awareness/knowledge of AAT deficiency higher than their colleagues in Italy did (68% vs 51% reporting that they had "very much" or "average" knowledge of the disorder). Fig. 3 shows the percentage of pulmonologists, IMs, and GPs who rated their extent of knowledge on AAT deficiency. Among pulmonologists, the proportion who reported knowing "very much" about the condition was 53% in Germany and 26% in Italy, compared with 5% and 1%, respectively, of GPs. Physicians in both countries were also questioned on where they obtained their information on AAT deficiency. German physicians reported to rely heavily on the scientific literature (78%), whereas Italian respondents were more likely to refer to textbooks (67%). Almost half of the respondents in Germany (49%) and 42% in Italy regarded scientific meetings and conferences as beneficial in communicating additional information on AAT deficiency.

Table 1 Composition of survey respondents by specialty, practice setting, and the average number of COPD patients seen per month.

	Germany (n = 180)	Italy (n = 181)
Specialty		
Pulmonology	(n = 60)	(n = 61)
Internal medicine specialist	(n = 60)	(n = 30)
GP	(n = 60)	(n = 90)
Practice setting		
Hospital	(n = 30)	(n = 91)
Pulmonology	(n = 30)	(n = 61)
Internal medicine specialist	—	(n = 30)
GP	—	—
Office	(n = 150)	(n = 90)
Pulmonology	(n = 30)	—
Internal medicine specialist	(n = 60)	—
GP	(n = 60)	(n = 90)
Average number of COPD patients/month		
Less than 5	(n = 8)	(n = 13)
6—20	(n = 42)	(n = 52)
21—50	(n = 69)	(n = 75)
More than 50	(n = 61)	(n = 41)

Testing for AAT deficiency

The percentage of physicians testing for AAT deficiency was found to be higher in Germany than in Italy. However, only half of all the physicians surveyed in Germany and 36% in Italy were testing patients regularly for the disorder. Regardless of country, pulmonologists and hospital-based physicians were seen to be driving AAT deficiency testing, as opposed to primary care physicians. Over 90% of physicians in Germany in these two groups currently test for AAT deficiency. Testing rates among IMs, GPs, and office-based physicians, on the other hand, were relatively low (Fig. 4). When participants in the two countries were asked how

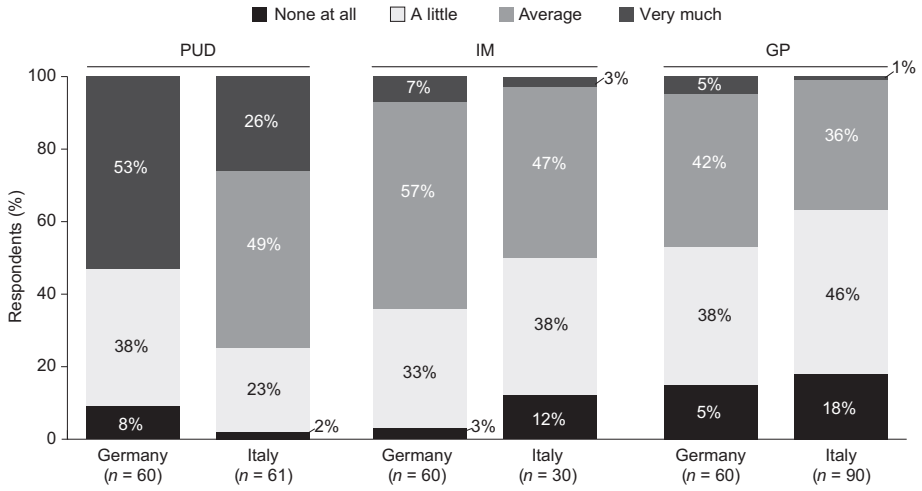

Figure 3 Knowledge of lung disease caused by AAT deficiency, by specialty.
Percentage of respondents from three different disciplines in Germany and Italy who gave the answer indicated to the question, *"How much do you know about lung disease caused by AAT deficiency?"*.
PUD — pulmonologists; IM — internal medicine specialists; GP — general practitioners.

often they tested for AAT deficiency, more than two-thirds (72% in Germany and 62% in Italy) reported carrying out between one and five tests per month. Moreover, the majority of physicians who were currently testing for AAT deficiency primarily tested young COPD patients (<45 years) and family members of AAT-deficient individuals. Only 18 and 25% of physicians in Italy and Germany, respectively, responded that they performed testing on all COPD and asthmatic patients (Table 2).

Reasons for not testing patients

When physicians who reported that they were not regularly testing for AAT deficiency were asked their reasons for this, the three most cited were: (1) the perception that the cost of testing was too high, (2) the view that they were rarely consulted by these patients, and (3) that patients with AAT deficiency would be referred to other specialists (Table 3). Only 7—8% of the physicians responded that there was no treatment available, and some cited uncertainty in the interpretation of the results as a reason for not testing for AAT deficiency (Germany, 10%; Italy, 6%; Table 3). Very few responded that they had tested but never positively identified any patients.

Physician communication with the laboratory regarding AAT deficiency testing

When the physicians who were currently testing for AAT deficiency were surveyed, all respondents regardless of their specialty or setting reported having good

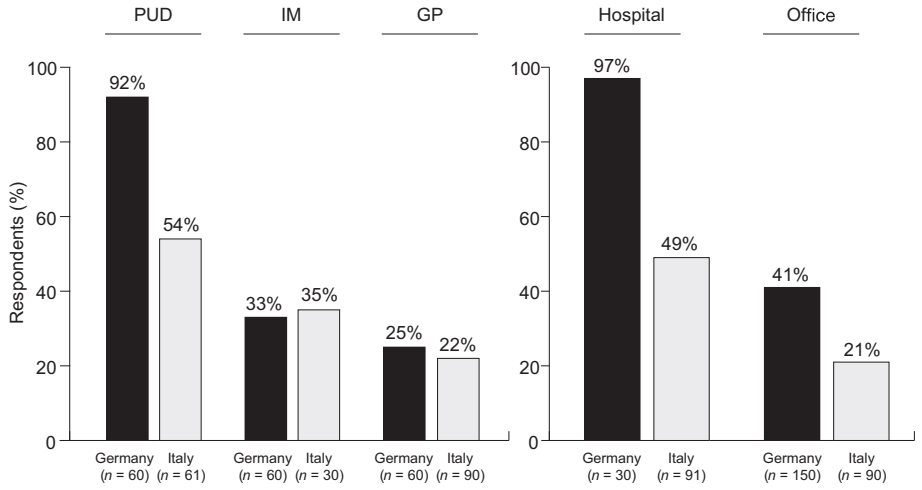

Figure 4 Physicians currently testing for AAT deficiency.
Percentage of respondents from three different disciplines in Germany and Italy who answered *"Yes"* to the question, *"Do you currently test for AAT deficiency?"*.
PUD — pulmonologists; IM — internal medicine specialists; GP — general practitioners.

Table 2 The types of patients most commonly tested for AAT deficiency by physicians.

Patient types tested for AAT deficiency	Germany Total (n = 90)	Italy Total (n = 65)
All COPD	18%	25%
Young COPD (<45 years)	83%	77%
Family members with AAT deficiency	69%	72%
Asthma	10%	23%
Bronchiectasis	39%	43%
Others	16%	17%

communication with the laboratory carrying out the tests (scoring, 3.3—3.4). There was, however, some disagreement (scoring, 2.6—3.0) with the statement that sufficient materials about the implications of a positive result for the patient were provided by the laboratory.

Physician communication with the patient regarding AAT deficiency testing

With regard to the genetic counseling of patients, there was little difference in attitudes between the physicians' disciplines (pulmonologist, IM, GP, hospital or office based) and the countries surveyed, none of whom felt either strongly comfortable or uncomfortable with communicating this information (scoring, 2.0—2.9). When it came to giving advice to patients about prognosis, lifestyle changes, and treatment, it was observed that, overall, the pulmonologists were more confident about giving the appropriate advice (Germany, 1.8; Italy, 2.2), while GPs were less sure about the right information and guidance to provide to these patients (Germany, 2.9; Italy, 3.1). There was a moderate perception among the disciplines in both countries that patients are lost to follow-up between initial screening and subsequent confirmatory tests (2.0—2.8).

Table 3 Reasons for not testing for AAT deficiency.

Respondents who do not test for AAT deficiency	Germany (n = 90)	Italy (n = 120)
Reason		
There is no treatment available for this disease	7%	8%
It takes too much time	14%	8%
The cost for testing is too high	31%	17%
I don't see those patients	26%	31%
I refer them to other specialists	51%	45%
Tested many but never found any	4%	4%
Interpretation of the test result is not clear	10%	6%
Other	4%	10%

The reasons given by German and Italian physicians who were not already testing for AAT deficiency are shown. The majority of respondents were internal medicine specialists and general practitioners, of whom many were office-based physicians.

Approaches to AAT deficiency testing

The survey results showed that physicians from both countries are following the same testing protocols. Most physicians expressed a clear tendency (66—70%) to perform serum level testing first and request further testing for severe deficiency in those individuals with reduced levels. The remainder either sent the samples to a laboratory specializing in AAT deficiency in Marburg or Pavia or to a commercial laboratory (Fig. 5).

Treatment of patients who are positively diagnosed

The physicians from both countries were asked whether they were currently treating their patients with augmentation therapy. Very few stated that all positively diagnosed patients were treated, however, approximately one-third of those surveyed from both Germany and Italy said that they sometimes offered this treatment.

Discussion

By evaluating the data from two national registries (Italy and Germany) and two reference laboratories (Pavia and Marburg), we can confirm that there is a significant delay for AAT-deficient patients between symptom onset and the time when the diagnosis is made, consistent with the existing literature.[14—17,19] Our data suggest that, compared with nonhereditary COPD, knowledge regarding AAT deficiency is relatively poor in Germany and Italy, particularly among internists and general practitioners. While current guidelines stress the need to test every COPD patient for AAT deficiency,[4,18] our data show that only 10—25% of physicians do so. We identified the main reasons for not testing to be the perception that AAT-deficient patients are not seen routinely, that they should be transferred to a specialist, and that testing procedures are too expensive. Taken together, our data provide reasons why AAT deficiency is still significantly under-recognized.

Among non-pulmonologists, the relatively low awareness of AAT deficiency in comparison with other respiratory diseases, as shown by our survey, is in accordance with the findings of other studies. Taliercio et al. (2010) reported that AAT deficiency may be overlooked by physicians, especially GPs.[29] Low disease awareness determines low testing rates, and several studies have demonstrated a low rate of testing and diagnosis for AAT deficiency.[15—17,25,30] Pulmonologists should encourage members of their extended multidisciplinary team to be alert to AAT deficiency. This might increase testing rates among GPs, internists, and other office-based physicians.

In the absence of a neonatal screening program for AAT deficiency in the general population, the opportunity to test for the disorder only arises when patients experience respiratory symptoms that prompt them to consult a physician. However, the symptoms of COPD due to AAT deficiency cannot be differentiated from those resulting from nonhereditary COPD or asthma. It is important,

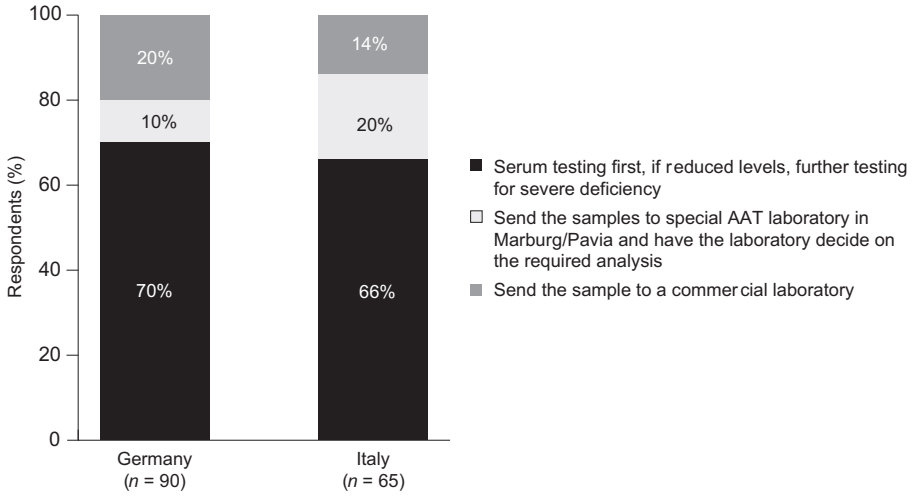

Figure 5 Preferred approaches for AAT deficiency testing.
Percentage of respondents from Germany and Italy who gave the answer indicated to the question, "*Which approach do you prefer?*".

therefore, for healthcare professionals to bear in mind that the diagnosis of AAT deficiency cannot be based on clinical presentation alone, and that a specific test must be undertaken. Guidelines state that all symptomatic patients with COPD, emphysema, or asthma with airflow obstruction that is not fully reversible should undergo specific testing for AAT deficiency.[4,18] However, our survey shows that the majority of physicians currently testing for AAT deficiency primarily test younger COPD patients (<45 years) and family members of AAT-deficient patients, with only 10—25% testing all patients with COPD and asthma. Evidently even those who are actively testing are not necessarily doing so in accordance with the recommendations, which may be due to a belief that COPD symptoms in younger patients are unusual, or that resources can be saved by testing only a minority of patients.

Although textbooks and other scientific literature were valuable sources of information for the countries surveyed here, exposure to information at congresses and meetings was also seen to be important for a large proportion of respondents. Development of training materials to help healthcare professionals understand AAT deficiency is therefore likely to be beneficial. A more interactive approach to continuing medical education programs, perhaps via web-based modules that provide physicians with feedback, or that allow them to compare their responses with those of their peers,[31] might give clinicians a greater awareness of the disorder. Such initiatives might help improve physicians' recall and acceptance of new challenges,[32] such as those posed by orphan diseases.

The full diagnostic protocol for AAT deficiency requires determination of both the patient genotype and phenotype (following the measurement of AAT levels in the blood), which can be time consuming. This is reflected in our registry data from Germany and Italy that showed once a test was initiated, the time needed to obtain a definitive diagnosis was in the order of 3—4 weeks. This considerable time interval was due to repeated blood sampling in some instances where there were errors with the initial collection process. Our results show that gene sequencing is associated with an increase in time to report a diagnosis when compared with genotyping alone. This delay was more pronounced in Germany, where such samples must be sent to another specialized laboratory. Furthermore, because the initial sample was a DBS, full blood had to be collected. For this reason, the test-initiating physician and the patient had to be contacted, which in some instances took more than a year. As a consequence, there is a time lag introduced, mainly due to contacting the physician and patient, the second collection of samples, the transportation of samples and communication of the result between laboratories.

Differences exist between countries in their approach to testing. In some countries, both genotyping and determination of the AAT concentration by nephelometry are done simultaneously by the laboratory. In other locations, genotyping is only carried out after the AAT level has been quantified and found to be below a certain cutoff (typically <1.0 g/L), which is more cost effective[33] but may incur a delay. This latter approach was favored by the majority of physicians surveyed (overall, 68—78%). A proportion of respondents (Germany, 20%; Italy, 14%) preferred to send patient samples for analysis to a decentralized commercial laboratory. Disseminating the information about preferred qualified testing laboratories might streamline screening protocols. Where standard algorithms are not practiced, there lies a risk that patients will become lost to follow-up during the course, for example, between initial serum level measurements and confirmatory tests. In the survey, over one-third of physicians in Germany and over half of physicians in Italy expressed the view that loss of patients to follow-up was an issue during AAT deficiency testing.

Previous reports have speculated that a further obstacle to the diagnosis of AAT deficiency may be the clinician's lack of conviction that effective treatments exist for the disorder,[29] or that it may be too complicated or inadequate.[19,34] However, this was not a major obstacle to testing for the clinicians surveyed in this study.

Whenever AAT deficiency is suspected, the physician must inform their patients of the need to be tested and

obtain their consent to carry it out; necessary steps which represent potential barriers to testing. Therefore, physicians' attitudes might represent a further barrier to the provision of more frequent testing, for example, their concerns surrounding the communication of information about a genetic disease to their patients and their general lack of training in genetic counseling.[35] In agreement with this, our survey showed that GPs, in particular, lacked some confidence when discussing these issues with their patients.

The purpose of testing is to identify affected patients, as well as family members, who either have AAT deficiency or are heterozygous carriers. Carriers may be at increased risk for developing lung or liver disease, and may be more vulnerable to these diseases if exposed to further risk factors, such as smoking and occupational hazards. It is important that affected patients disclose their diagnoses to family members. Studies of a Swedish cohort of AAT-deficient individuals who were diagnosed at birth[8] revealed that antismoking advice given later in life was relatively successful; only a small proportion of individuals (3% of questionnaire respondents) with confirmed PiS or PiZ AAT deficiency started smoking as adults.[36] In addition, when compared with a non-AAT-deficient control group, patients who had been diagnosed with AAT deficiency at birth were significantly less likely to become smokers as adults ($p < 0.05$)[37] One can speculate that knowledge about their disease prompted a behavioral response among the AAT-deficient cohort which reduced the likelihood of them starting to smoke. This illustrates the importance of making genetic counseling widely available in conjunction with testing, and here physicians can play a critical role.[38]

Although not cited as a major barrier in this study, in some instances, low rates of testing might reflect a degree of "testing fatigue" among clinicians,[32] where they perceive that routinely testing vast numbers of patients will yield few positive results. However, when a targeted approach is taken, which tests individuals who have COPD, incompletely reversible responsive asthma, liver disease, or if there is a family member with AAT deficiency, the detection rate is elevated. A recent screen for AAT-deficient patients in Ireland identified that, within the general population, 14.8% of individuals had at least one alpha$_1$-PI gene mutation, and this figure was almost doubled (27.1%) when targeted testing was undertaken.[11] It is predicted, therefore, that by screening all patients with COPD, of whom an estimated 1–3% are expected to have AAT deficiency,[15] many more patients would be identified.

There still appears to be a widespread lack of awareness about this disorder. Our data suggest that respiratory specialists and other healthcare professionals continue to face hurdles in the testing and diagnosis of patients. An increase in physician education about AAT deficiency, and the use of simpler testing approaches, should prove beneficial and will undoubtedly lead to more patients being identified.[20]

In summary, we confirm earlier data that show a significant delay for AAT deficiency patients between the onset of symptoms and time of diagnosis. Reasons for this include limited awareness and knowledge about AAT deficiency, the finding that only a minority of physicians test in accordance with recommended practice, as well as a number of issues relating to the interpretation of test results. With a greater understanding of the hurdles that stand in the way of diagnosing patients with AAT deficiency, it might be possible to reduce time delays, enable patients to avoid risk factors and commence therapy earlier.

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Author contributions

T. Greulich and I. Ferrarotti made equal contributions to the design and conception of the study, analysis and interpretation of the data, and drafting of the manuscript. All other authors critically reviewed and approved the final manuscript.

Disclosure of potential conflicts of interest

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Appendix A. Supplementary information

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