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## Diagnosis and management of $\alpha$ 1-antitrypsin deficiency in Europe: an expert survey.

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# Diagnosis and management of $\alpha_1$ -antitrypsin deficiency in Europe: an expert survey

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**ABSTRACT** Despite recent improvements,  $\alpha_1$ -antitrypsin deficiency (AATD) remains a rarely diagnosed and treated condition. To assess the variability of AATD diagnosis/treatment in Europe, and to evaluate clinicians' views on methods to optimise management, specialist AATD clinicians were invited to complete a web-based survey.

Surveys were completed by 15 physicians from 14 centres in 13 European countries. All respondents perceived the AATD diagnosis rate to be low in their country; 77% of physicians believed that ~15% of cases were diagnosed. Low awareness was perceived as the greatest barrier to diagnosis. Spirometry was considered more practical than quantitative computed tomography (QCT) for monitoring AATD patients in clinical practice; QCT was considered more useful in trials. AAT therapy provision was reported to be highly variable: France and Germany were reported to treat the highest proportion (~60%) of diagnosed patients, in contrast to the UK and Hungary, where virtually no patients receive AAT therapy. Most clinicians supported self-administration and extended dosing intervals to improve convenience of AAT therapy.

This survey indicates that AATD diagnosis and management are highly heterogeneous in Europe; European cooperation is essential to generate data to support access to AAT therapy. Improving convenience of AAT therapy is an ongoing objective.



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Access to  $\alpha_1$ -antitrypsin ( $\alpha_1$ -AT) therapy varies in Europe; where available,  $\alpha_1$ -AT therapy optimisation is the goal <http://ow.ly/YL6m30n4LV3>

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## Introduction

$\alpha_1$ -Antitrypsin deficiency (AATD) is a well-established, but underdiagnosed inherited condition that can lead to emphysema and liver disease. It is caused by mutations in the *SERPINA1* gene encoding  $\alpha_1$ -antitrypsin (AAT), a key serum protease inhibitor. In individuals with AATD, serine proteases, primarily neutrophil elastase, are not inhibited, resulting in degradation of lung tissue and eventual progression to emphysema [1]. In addition, patients with the Z variant or rare variants such as M<sub>Malton</sub> or S<sub>Iiyam</sub> have an increased risk of developing liver disease, owing to protein accumulation in hepatocytes [1].

Multiple factors contribute to the underdiagnosis of AATD, including similarities in presentation to general chronic obstructive pulmonary disease (COPD) and asthma and lack of access to testing, with low disease awareness perhaps the key issue [2–5]. Targeted detection programmes aimed at symptomatic individuals, e.g. COPD patients, and neonatal screening have been employed in Europe and have helped to increase diagnosis rates [6–8]. However, active screening programmes for AATD do not exist in many countries and numerous patients in Europe remain undiagnosed. Due to the progressive and irreversible destruction of lung architecture in AATD, early detection is essential to enable lifestyle modifications (e.g. smoking cessation) and appropriate treatment [9].

COPD related to AATD is managed symptomatically with bronchodilators [10], in line with non-AATD-associated COPD. However, purified human AAT is the only disease-modifying therapy currently available that can slow progression of emphysema related to AATD [11, 12]. Currently, the therapy is recommended only for patients with severe deficiency genotypes, e.g. PI\*ZZ (European Respiratory Society (ERS) guidelines and US guidelines) and PI\*SZ (US guidelines only) [13, 14]. The optimal time for treatment initiation has been greatly debated. Recent US guidelines suggest that *i.v.* AAT therapy can be considered in symptomatic individuals at any level of spirometric impairment, as determined by forced expiratory volume in 1 s (FEV<sub>1</sub>) % predicted, although the strongest recommendation for treatment is when FEV<sub>1</sub> is  $\leq 65\%$  pred [13]. The recent ERS statement does not specify a threshold for treatment [14]. The 2003 statement from the American Thoracic Society (ATS) and ERS recommended AAT therapy in patients with moderate airflow obstruction (e.g. FEV<sub>1</sub> 35–60% pred), because historically there is more evidence of an effect on spirometric decline in this range [1].

Current trends are moving towards a personalised approach to AAT therapy provision [15], with pharmacokinetic models demonstrating that extended dosing intervals are feasible [16]. Despite this, there are few recommendations on methods to improve convenience of *i.v.* dosing regimens, e.g. extended-interval dosing and self-administration. However, in many European countries, accessing AAT therapy is the principal challenge – half the European countries surveyed in the latest ERS statement reported having no access or very limited access to treatment [14].

To gain an understanding of the current status of AATD diagnosis and management in Europe, as well as attitudes towards methods for AAT therapy optimisation, we performed a survey of European AATD experts.

## Materials and methods

### Data collection

Clinicians treating AATD from across Europe were invited to complete a web-based survey. The objective was to gather expert opinion on the diagnosis and management of patients with AATD. The survey consisted of 58 questions covering 1) size of patient population; 2) diagnosis and management of AATD; 3) AATD treatment options; 4) dosing of AAT therapy; and 5) self-administration and home treatment with AAT therapy. Self-administration was defined as *i.v.* administration of AAT performed by the patient or a non-professional (e.g. assistance from a spouse or relative). Home treatment was defined as *i.v.* administration of AAT performed by a healthcare professional (e.g. physician or nurse).

### Data analysis

Descriptive statistics only are reported; no formal statistical tests were performed.

## Results

### Survey representation

Completed surveys were returned by 15 physicians from 14 centres in 13 countries: Austria, Belgium, Czech Republic, France, Germany, Hungary, Ireland, Italy, the Netherlands, Poland, Portugal, Spain and the UK. All respondents are responsible for managing and treating patients with severe AATD genotypes, e.g. PI\*ZZ.

### Diagnosis of AATD

Physicians' estimates of the number of diagnosed AATD cases varied greatly between countries and were generally far lower than the number of individuals with severe AATD in each country based on published estimates (table 1) [17, 18]. All respondents perceived the rate of diagnosis to be low in their countries:

TABLE 1 Testing for  $\alpha_1$ -antitrypsin deficiency (AATD) and the estimated number of cases in Europe

	National AATD treatment infrastructure		Estimated number of diagnosed AATD cases versus overall number of severe deficiency carriers		
	Nationwide active screening programme	Treatment centres with >10 patients n	Estimated diagnosed severe AATD cases n	Individuals with severe AATD genotype <sup>#</sup>	
				Based on epidemiological studies [17]	Mathematically derived [18]
Austria	No	≥5	250	1435 (607–3318)	1529 (646–3536)
Belgium	No	3	100	2896 (1583–5249)	2917
Czech Republic	No	1	70	N/D	N/D
France	No	≥5	≥1000	9982 (7662–12 989)	17 191 (13 255–22 270)
Germany	No	≥5	≥1000	8003 (5520–11 577)	20 611 (13 380–31 626)
Hungary	Yes	0	≤50	458 (149–1352)	N/D
Ireland	Yes	0	300	N/D	2265 (1264–4019)
Italy	No	1	500	15 659 (2864–19 150)	10 652 (7046–16 049)
The Netherlands	No	1	500	1711 (976–2980)	5353 (3057–9298)
Poland	Yes	1	100	662 (421–1039)	6791 (4395–10 454)
Portugal	No	3	150 <sup>¶</sup>	2005 (1054–3774)	4944 (2403–10 004)
Spain	Yes	4	650	12 045 (7801–18 522)	14 522 (9405–22 331)
UK	No	3	2100	8588 (5906–12 458) <sup>†</sup>	England: 11 939 (7729–18 360) Scotland: 344 (182–644)

Data are presented as n [95% CI], unless otherwise stated. N/D: no data. <sup>#</sup>: PI\*ZZ genotype only; <sup>¶</sup>: averaged response from two respondents; <sup>†</sup>: not including Wales.

77% of physicians believed that ~15% of cases had been diagnosed, with the remainder estimating a 30% diagnosis rate. Few AATD screening programmes were reported in Europe (table 1); all respondents had access to AAT serum level testing and phenotyping (isoelectric focusing), 93% had access to targeted genotyping for common deficiency variants and 73% had access to *SERPINA1* gene sequencing (to identify rare/novel/null variants). The majority of physicians (60%) estimated that on average it took ≥5 years to obtain a diagnosis of AATD from first onset of symptoms (figure 1a); lack of awareness was most frequently cited as the biggest barrier to AATD diagnosis (77% of physicians) (figure 1b).

**Treatment and monitoring of AATD**

Across Europe, patients with AATD were reported to be symptomatically managed principally with long-acting  $\beta$ -adrenergic receptor agonists, long-acting muscarinic receptor agonists and inhaled corticosteroids. Provision of AAT therapy is highly variable throughout Europe. France and Germany were reported to have the highest proportions of diagnosed AATD patients receiving AAT therapy (60%); in Spain, ~20% of patients receive treatment with AAT (figure 2).

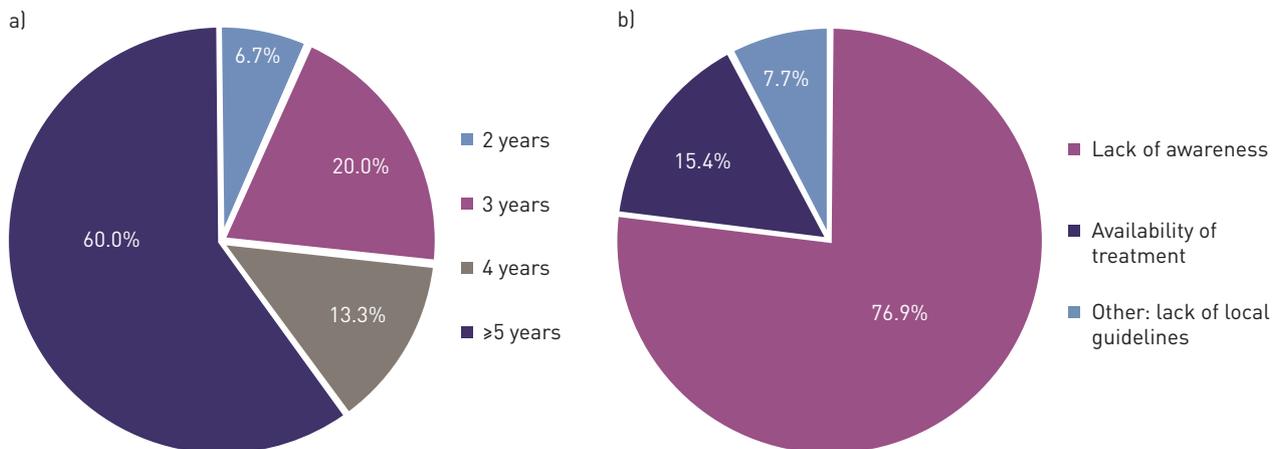
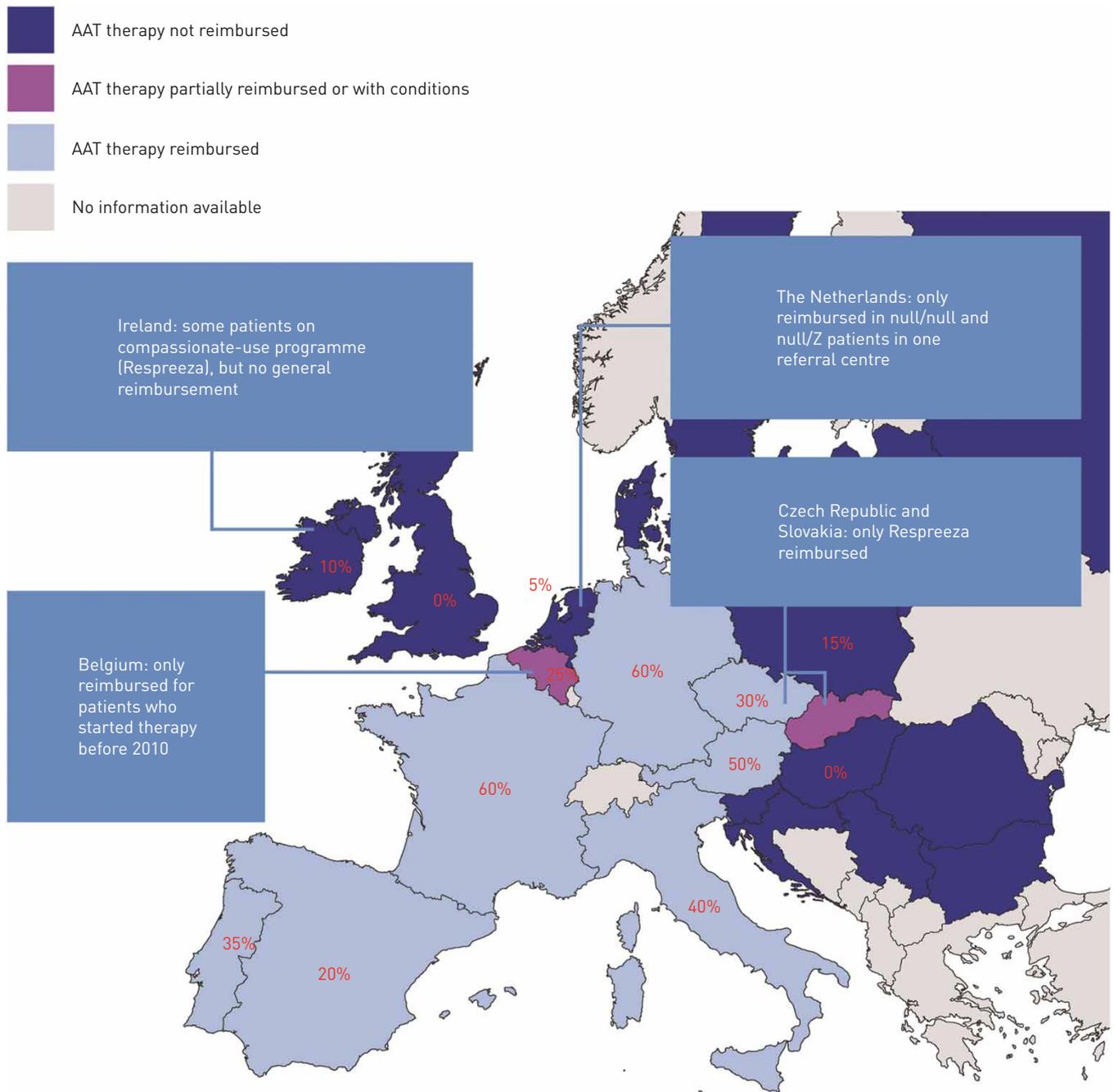
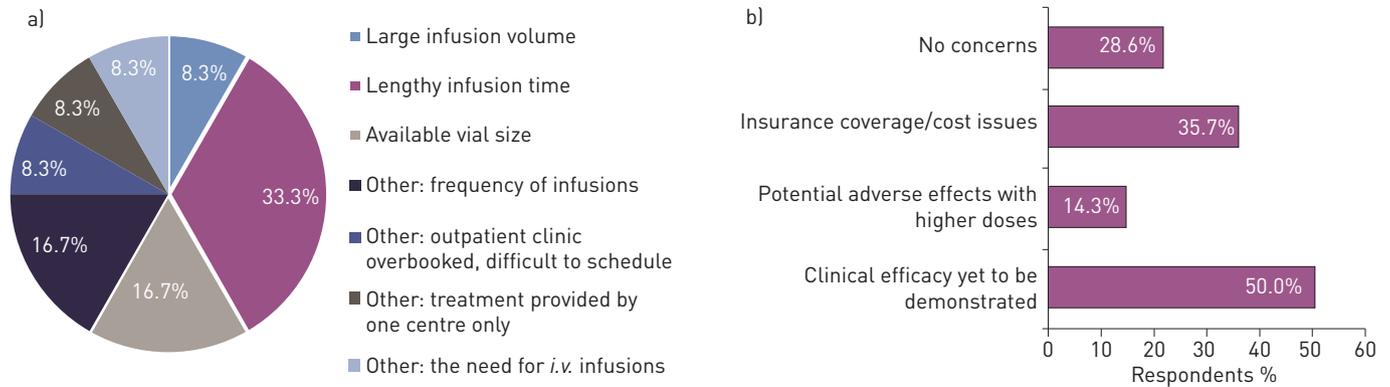


FIGURE 1 a) Estimated number of years to obtain formal diagnosis of  $\alpha_1$ -antitrypsin deficiency (AATD), from first onset of symptoms; b) barriers to diagnosis of AATD in Europe.



Product	Countries with regulatory approval
Alfalastin	France
Prolastin	Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Ireland, Italy, the Netherlands, Norway, Poland, Portugal, Slovakia, Spain, Sweden and Switzerland
Respreeza	EU-wide

FIGURE 2  $\alpha_1$ -Antitrypsin (AAT) therapy availability across Europe. Reimbursement data obtained from European Respiratory Society 2017 statement [14]. Data are presented as percentage of diagnosed patients on AAT therapy; values based on individual physician estimates. Portugal figure represents the average of two responses.



**FIGURE 3**  $\alpha_1$ -Antitrypsin (AAT) therapy considerations: a) practical difficulties with AAT infusions; b) concerns regarding AAT doses  $>60 \text{ mg}\cdot\text{kg}^{-1}$  per week. Data are presented as percentage of respondents; physicians could choose more than one concern regarding AAT doses  $>60 \text{ mg}\cdot\text{kg}^{-1}$ . No AAT products were specified and there was no agreed definition on what constituted a lengthy infusion time.

#### AAT therapy considerations

Practical challenges with AAT infusions were reported, the most often cited being infusion time (33%; figure 3a). The majority of respondents (73%) would consider alternative dosing strategies (e.g. bi-weekly dosing); reasons included to cover holidays and for individuals in full-time employment. This practice is already employed in some countries, e.g. all patients in the Czech Republic receive bi-weekly dosing, and it is an option in France and Spain. Most respondents (87%) would consider providing AAT doses higher than the recommended weekly dose of  $60 \text{ mg}\cdot\text{kg}^{-1}$  in some situations, such as when the “protective threshold” for AAT serum level was not reached, during exacerbations and for patients with rapidly deteriorating disease. The main concern regarding higher doses was the lack of proven clinical efficacy; however, nearly one-third of respondents (29%) had no concerns (figure 3b).

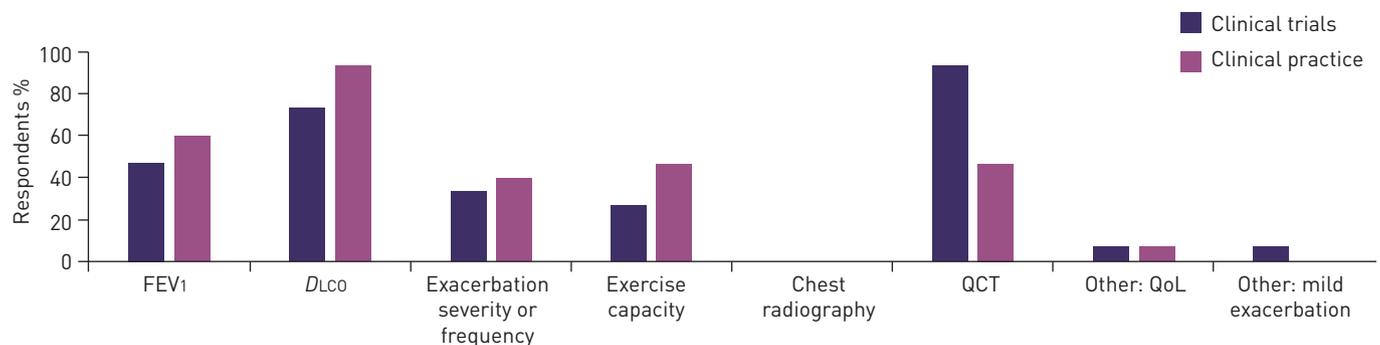
#### Monitoring of AATD

Physicians were asked what they perceived to be the most useful methods for monitoring disease progression and treatment efficacy in diagnosed AATD patients (figure 4). Quantitative computed tomography (QCT) of the lungs, i.e. measurement of lung density, was viewed as the most useful measure in clinical trial settings. Diffusing capacity of the lung for carbon monoxide (DLCO) was considered the most useful measure for monitoring AATD in routine clinical practice, but less useful in clinical trials. Some physicians commented that DLCO can be very informative in trials involving fewer or single centres. FEV<sub>1</sub> was considered less useful than QCT and DLCO in trials, but more practical than QCT in routine clinical practice.

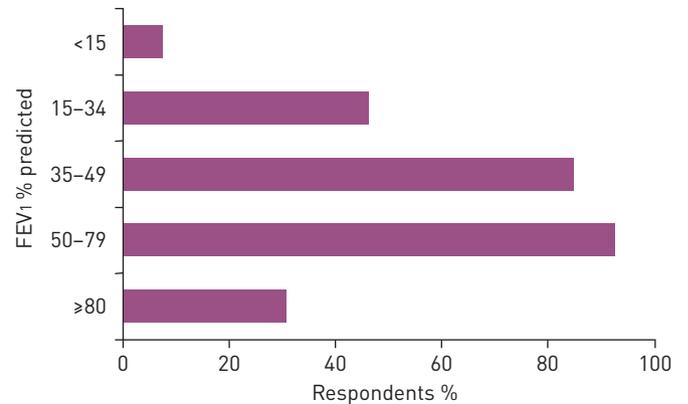
#### Optimising treatment of AATD

##### Timing of treatment initiation

Most physicians surveyed would consider using AAT therapy in patients with moderate disease severity, i.e. FEV<sub>1</sub>  $<80\%$  and  $\geq 35\%$  pred (figure 5). A minority would consider AAT in early- and late-/end-stage disease (FEV<sub>1</sub>  $\geq 80\%$  and  $<35\%$  pred). Some physicians commented that in patients with severe AATD and



**FIGURE 4** Physician perspectives on the most useful methods for monitoring  $\alpha_1$ -antitrypsin deficiency in the clinical trial setting versus clinical practice. FEV<sub>1</sub>: forced expiratory volume in 1 s; DLCO: diffusing capacity of the lung for carbon monoxide; QCT: quantitative computed tomography; QoL: quality of life.



**FIGURE 5** Degree of lung function impairment at which physicians would consider commencing  $\alpha_1$ -antitrypsin therapy. FEV1: forced expiratory volume in 1 s.

FEV1 above the historically recommended range for treatment (FEV1 35–60% pred) [1], QCT should be used to confirm the presence, severity and distribution of emphysema.

#### Self-administration

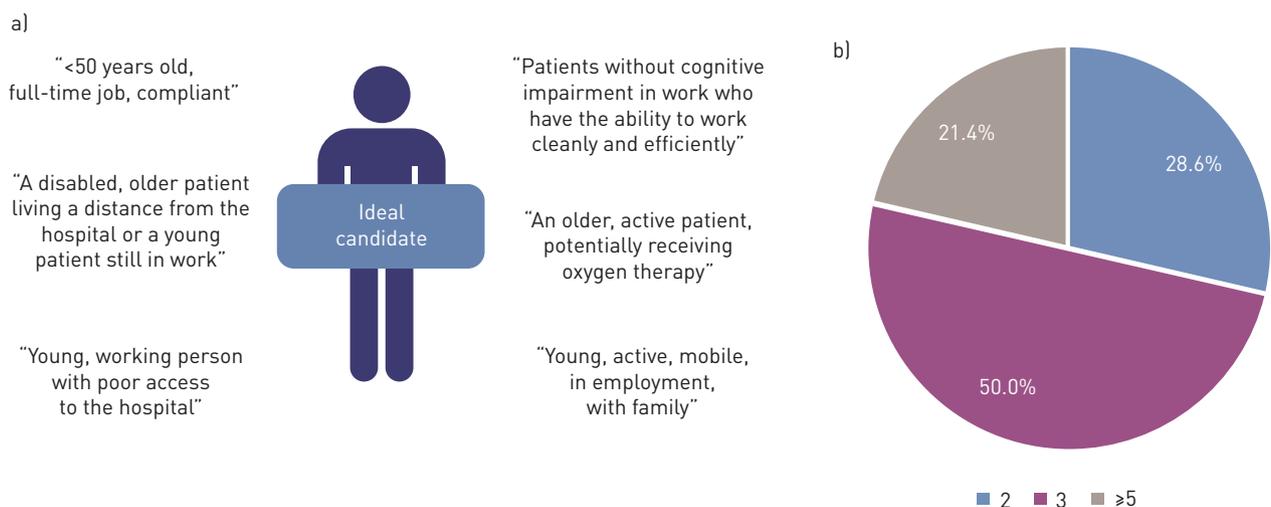
Self-administration of *i.v.* AAT was not available in any of the countries surveyed. However, all respondents would consider self-administration for some patients if it were available. Respondents suggested that a number of patient groups would benefit from self-administration, *e.g.* those in employment (figure 6a). Overall, ~50% of respondents felt that for patients to self-administer independently, three training sessions would be required (figure 6b); 86% of respondents felt that training should be provided by hospital-based respiratory nurses. Greater independence was viewed as the most important advantage of self-administration; safety issues surrounding *i.v.* administration were viewed as the main disadvantage.

#### Home treatment

Home treatment was available in four of the countries surveyed (Ireland, France, Poland, Czech Republic), provided by trained community nurses, but only as part of clinical trials in Ireland and Poland. Home therapy is the only treatment option in Ireland and France; in Poland, regular treatment is provided at home, but is also available at hospital outpatient clinics. Convenience for the patient was viewed as the most important advantage of home treatment; fewer resources available in the event of an emergency was most frequently cited as the main disadvantage.

### Discussion

This survey of experienced clinicians treating AATD indicates that levels of diagnosis and disease awareness in Europe remain low. Furthermore, there is great variability across Europe in the provision of AAT therapy, the only pharmacological intervention able to slow emphysema progression related to AATD.



**FIGURE 6** Physician perspectives on self-administration of *i.v.*  $\alpha_1$ -antitrypsin. a) The ideal candidate for self-administration; b) the number of training sessions required for a patient to self-administer independently. Data are presented as percentage of respondents.

Published reports [17, 18] provide high estimates of the number of PI\*ZZ carriers in Europe; although these do not reflect the number of symptomatic cases, the estimated numbers of diagnosed cases reported in our survey are lower than might be expected. This disparity may be due to the number of patients who are currently asymptomatic [19]; however, it is likely that many patients are misdiagnosed or face delays in diagnosis [2, 4]. Most physicians surveyed believed that only 15% of AATD cases had been identified, and that a confirmed diagnosis of AATD takes >5 years to obtain. A similar scenario was reported in Canada, with a delay in diagnosis of 7 years [20]. Our survey suggests that low awareness remains the biggest contributor to underdiagnosis/delay in diagnosis in Europe, consistent with previous studies [4, 5, 21]. In Europe, an overarching issue is that awareness and detection in primary care are very low, with few physicians referring patients for AATD testing [4, 21]. Nevertheless, there have been successes with public health campaigns focused on improving diagnosis. For example, in Germany, a disease-awareness campaign coupled with AATD testing dramatically improved AATD detection [6].

Although AATD screening programmes in Europe have helped to increase detection of AATD and improve access to AAT therapy [7, 22–25], only four national screening programmes were reported in our survey (table 1). There are several screening strategies for AATD, including population-based screening, targeted screening of COPD patients, testing patients with liver disease and familial screening. Population-based screening is uncommon and one of the few implementations of this approach was the neonatal screening programme employed by Sweden in the 1970s. This programme provided important insights into the natural history of AATD and the variability of presentation; in addition, awareness of the condition enabled patients to avoid respiratory risk factors, *e.g.* smoking [7]. However, population-based screening programmes can be prohibitively expensive and therefore their use has been limited to high-risk areas, *e.g.* in remote/isolated communities [26]. Currently, targeted screening programmes are viewed as the most feasible and economically viable approach [24], with these enriched populations leading to far higher AATD detection rates [8]. Guidelines recommend that several respiratory conditions (*e.g.* emphysema, bronchiectasis) and nonrespiratory conditions (*e.g.* liver disease, panniculitis) should trigger testing, and the strongest universal recommendation is to test all newly diagnosed COPD patients [1, 13, 27, 28]. Furthermore, owing to Mendelian inheritance, familial screening provides the highest likelihood of uncovering additional AATD cases. All guidelines advocate familial testing, with testing of siblings being the highest priority [1, 13, 14]. Testing recommendations from guidelines/statements are outlined in table 2.

Regarding monitoring of disease progression in AATD, the recent ERS statement suggests that patients be assessed regularly by a multidisciplinary team in the first year after diagnosis [14]. Our survey revealed lung function testing *via* DLCO and FEV<sub>1</sub> to be central to AATD monitoring in European clinics. This is in line with available guidance (table 2) [1, 13]. A recommendation in guidelines from the US Alpha-1 Foundation is to conduct a baseline computed tomography (CT) scan as part of the initial assessment of AATD patients [13]. The guidelines do not recommend serial CT scanning owing to the associated radiation dosage and a lack of clarity on how best to use scan data for clinical management. Survey respondents generally felt that QCT was more suited to studies in AATD, and less applicable in clinical practice. Although lung densitometry by CT has been validated against lung pathology/function and health status, and has been the main outcome measure in clinical trials of AAT therapy, there are practical issues that reduce its applicability to routine practice [29]. Many centres do not have the requisite equipment/software to routinely conduct lung density assessment [9]. However, lung density data from clinical practice, such as that collated by the UK Antitrypsin Deficiency Assessment and Programme for Treatment (ADAPT) registry [30], have been extremely useful for research purposes, and could help to enhance the evidence base for AAT therapy. Regarding other approaches, some respondents indicated that monitoring quality of life was beneficial. Data from a recent meta-analysis indicate a possibility that AAT therapy has some efficacy on St George's Respiratory Questionnaire (SGRQ), a commonly used quality-of-life measure in respiratory disease [31]. However, this finding was associated with considerable uncertainty and further studies are required.

One aim of our survey was to assess how and when physicians utilise AAT therapy. Currently, AAT therapy is recommended only for symptomatic AATD patients, *e.g.* patients with airflow obstruction and physiological signs of emphysema [1, 13]. The ATS/ERS statement from 2003 recommended that therapy be utilised between a defined range of FEV<sub>1</sub> deterioration (35–60% pred); however, today there is less emphasis placed on FEV<sub>1</sub> ranges, and the recent ERS statement does not refer to this as a criterion for treatment [14]. Nonetheless, insurance coverage may still be linked to FEV<sub>1</sub> deterioration, and most physicians surveyed would not consider treatment at all levels of FEV<sub>1</sub> decline. However, some respondents would consider providing AAT in early-stage disease. Recent evidence provides a strong rationale for early intervention in AATD: data from the RAPID clinical trial programme suggest improved outcomes with early AAT therapy, with a discernible effect on lung density decline observed regardless of baseline FEV<sub>1</sub> [12, 32, 33].

TABLE 2 Comparison of recommendations from American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines (2003), US Alpha-1 Foundation guidelines (2016) and ERS statement (2017)

	ATS/ERS statement (2003) [1]	US Alpha-1 Foundation guidelines (2016) [13]	ERS statement (2017) [14]
<b>Diagnostic tests</b>	AAT serum levels should not be viewed in isolation Phenotyping or targeted genotyping may be utilised Phenotyping may be insufficient to detect rare variants and sequencing may be required	Targeted genotyping for S and Z alleles as a minimum Initial tests can be confirmed by phenotyping, quantitation of AAT serum levels and/or expanded targeted genotyping	Establishing AAT serum levels is a crucial first test, but must be supported by qualitative evidence of a mutation Phenotyping and genotyping can both be used to establish mutation(s) present Gene sequencing is necessary when a null or rare variant is suspected
<b>Who should be tested?</b>			
Testing for index case	Emphysema with early onset (<45 years) or without recognised risk factors, e.g. smoking, or with basilar hyperlucency Bronchiectasis or liver disease with unknown aetiology Necrotising panniculitis and anti-proteinase 3-positive vasculitis Family history of emphysema, bronchiectasis, panniculitis or liver disease	COPD or unexplained bronchiectasis, regardless of age/ethnicity All individuals with liver disease of unknown aetiology All patients with granulomatosis with polyangiitis/necrotizing panniculitis	COPD or adult-onset asthma
Familial testing	Recommended for siblings of index cases with severe deficiency Should be discussed with offspring or distant relatives of individuals with severe deficiency, and siblings, offspring, parents and distant relatives of individuals with intermediate deficiency	Parents, sibling, offspring and extended family should be offered genetic counselling and testing AAT level testing alone is not recommended when testing family members	Test parents of index case only if a null gene is suspected Test partner of index case; if PI*MZ is found, test offspring of index case Test sibling(s) of index case; if PI*MZ is found, test partner of sibling(s), if further PI*MZ is found, test offspring of sibling(s)
Population screening	Screening of any age group should be discouraged; screening of active smokers with normal spirometry is not recommended		
<b>Monitoring</b>	Full lung function testing at baseline and spirometry at yearly intervals Regular liver function testing requires investigation	Baseline and annual spirometry CT scan at baseline; serial CT scanning not recommended Monitor for liver disease annually: liver ultrasound and AST, ALT, GGT, albumin, bilirubin and INR	Importance of multidisciplinary approach highlighted Baseline: assess lung physiology and conduct routine liver function and blood tests Up to 3 months: reassess and collate data; monitor exacerbation diary, initiate smoking cessation Up to 6 months: assess full physiology, QoL assessment, routine blood tests 6–12 months: continue monitoring, initiate AAT therapy as appropriate FEV <sub>1</sub> and DLCO are useful to monitor disease progression
<b>AAT therapy utilisation</b>			
Recommended	Symptomatic individuals with FEV <sub>1</sub> 35–65% pred	Symptomatic individuals with FEV <sub>1</sub> ≤65% pred (strongest recommendation); treatment can be considered outside of this range	Symptomatic individuals (no FEV <sub>1</sub> range given)
Not recommended	PI*MZ individuals and current smokers	PI*MZ and current smokers Emphysema/ bronchiectasis without airflow obstruction	PI*MZ, PI*SZ and current smokers
AAT: α <sub>1</sub> -antitrypsin; COPD: chronic obstructive pulmonary disease; CT: computed tomography; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: γ-glutamyltransferase; INR: international normalised ratio; QoL: quality of life; FEV <sub>1</sub> : forced expiratory volume in 1 s; DLCO: diffusing capacity of the lung for carbon monoxide			

The standard dose for AAT therapy is 60 mg·kg<sup>-1</sup> per week; higher AAT doses are not currently licensed or recommended. However, this survey indicates that some physicians would consider providing higher doses, *e.g.* at times of exacerbation or for patients with fast-declining lung function. There is increasing interest in higher AAT doses: a recent pilot study found that normalising serum AAT levels in AATD patients by increasing dosing from 60 to 120 mg·kg<sup>-1</sup> per week further reduced markers of residual proteolytic and inflammatory activity [34]. In addition, an analysis of patients who received 120 mg·kg<sup>-1</sup> AAT or placebo to cover 2-week periods in the RAPID clinical trial programme found no increase in the infusion-adjusted event rate at 24 h and 72 h after administration [35]. The clinical utility and long-term safety of higher doses require further study and trials are ongoing.

This survey highlights that access to AAT therapy is not uniform throughout Europe, with some countries reporting that no diagnosed AATD patients receive AAT therapy. Indeed, the recent ERS statement suggests that reimbursement is an ongoing challenge in Europe (figure 2) [14]. The European situation reflects the Canadian experience, where large disparities in the provision of AAT therapy were observed between provinces [20]. Within the European Union (EU), policies exist to support equal access to novel therapies between countries. For example, directive 89/105/EEC6 states that pricing and reimbursement decisions must be made in a timely and transparent manner [36]. Nevertheless, these decisions are ultimately at the discretion of member states according to their independent appraisal of the technology and budgetary requirements [37]. In addition, although EU policies support cross-border diagnosis and treatment in rare diseases (EU directive 2011/24/EU), the health authority or insurance provider in the home country must agree to reimburse treatment in the destination country [37]. This issue, coupled with the impracticality of travelling abroad for medical treatment, suggests that cross-border treatment is not a long-term solution to address variation in access to AAT therapy in Europe.

Continuing to build the evidence base for AAT therapy is essential to support access to treatment. The RAPID clinical trial programme demonstrated that AAT therapy is effective and disease-modifying in AATD [11, 12, 33]. Beyond this, some authorities desire data on patient-centred outcomes, *e.g.* mortality and QoL, to support the pharmaco-economic profile of AAT therapy [38]. However, it is difficult to generate these data in clinical trials, as large numbers of AATD patients would have to be followed for long durations. Patient registries in Europe are therefore crucial in gathering longitudinal data of the efficacy of AAT therapy on these outcomes [14].

Where AAT therapy is available, improving convenience is a key challenge. Alternative dosing strategies (*e.g.* bi-weekly) and home treatment are already used in some European countries [28, 39]. In addition to the national home treatment programmes reported here, a third party-sponsored Berlin-based programme in Germany has reported successful results in terms of improving patient monitoring and reducing exacerbation-related hospitalisations in a small pilot study [40]. Self-administration is likely to be beneficial for subsets of AATD patients and could help reduce costs associated with treatment. Self-administration with increased intervals between infusions has been trialled in AATD and reduced the annual cost of AAT therapy [41]. Furthermore, self-administration is performed safely in other disease areas, such as haemophilia and immunoglobulin deficiencies [42, 43]. Overall, the physicians surveyed supported these measures to help improve convenience for patients.

### Limitations

Data were gathered from a survey of AATD experts and do not represent clinical findings. All data (unless otherwise specified) are estimates based on individual physician experience, and do not necessarily reflect actual regional policy and patient demographics. Nevertheless, all physicians selected for the survey were experts in the field of AATD, and were thus well positioned to provide an overview of the status of AATD diagnosis/management in their respective countries based on their clinical experience. Although a good cross-section of Europe is represented, in most cases, only one expert physician from each country returned a response. Further studies including more responses from each country would be required to verify the data.

### Conclusions

This physician survey strongly indicates that AATD remains underdiagnosed and undertreated in Europe. More initiatives are required to support disease awareness and encourage screening of individuals with COPD, adult-onset asthma or bronchiectasis and family members of diagnosed patients. The availability of AAT therapy varies greatly between European countries; cooperation is essential to generate data that could support access to treatment, and to raise awareness of successes in countries where the treatment is available. Improving convenience of AAT therapy is an ongoing objective.

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