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Research Priorities in alpha-1 antitrypsin deficiency: Results of a patients' and healthcare providers' international survey from the EARCO Clinical Research Collaboration

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ABSTRACT

Introduction: Alpha-1 antitrypsin deficiency (AATD) is a rare and under-recognized genetic condition. Due to its low prevalence, international initiatives are key to conduct high quality research in the field.

Method: From July 2018 to December 2019, EARCO (European Alpha-1 Research Collaboration) developed and conducted two surveys, one for health care professionals (HCP) and one for patients and caregivers aiming to identify research priorities and barriers in access to treatment in AATD.

Results: A survey on 164 research questions was electronically sent to 230 AATD experts in Europe, and 94 completed questionnaires from 24 countries were received. The top questions identified by HCP were: causes of variable progression and poor outcomes, improvement in diagnosis, initiation and optimal dosing of augmentation therapy and effectiveness of self-management interventions. During the same period, a total of 438 questionnaires were completed by patients and caregivers from 26 countries. The top research areas identified were: improving knowledge about AATD, in particular among general practitioners, access to AATD specialised centres and to reliable, easy to understand information about living with AATD. Regarding barriers to treatment, participants from countries where augmentation therapy was reimbursed prioritized also improving knowledge in AATD, while for respondents in non reimbursed countries access to AATD augmentation therapy and to specialised centres were the most relevant.

Conclusion: The main research and management priorities identified by HCPs and patients included understanding the natural history of AATD; improving information to physicians, access to specialized, reference centers; personalizing the treatment and having equal opportunities for access to existing therapies.

KEYWORDS

Alpha-1 antitrypsin deficiency, survey, patient-centered

INTRODUCTION

Alpha-1 antitrypsin deficiency (AATD) is an under-recognized genetic condition that affects approximately 1 in 2000 to 1 in 5000 individuals and predisposes to early-onset emphysema and liver disease (1). Due to its low prevalence AATD is considered a rare disease and because of the variety of its clinical manifestations many patients may remain undiagnosed until they develop a severe respiratory or liver disease.

A recent statement on AATD by the European Respiratory Society (ERS) (2) recommended organizing the care of patients in reference centers due to the low prevalence of the disease. Reference centers must establish a registry of their activity that enables them to share data concerning clinical characteristics and natural history of patients, nationally and internationally. In this context, the European Alpha-1 Research Collaboration (EARCO) was created in 2018 (3) as a Clinical Research Collaboration (CRC) of the ERS (4) composed by a group of international experienced and new researchers in the field of AATD, committed to promote research in the different aspects of the disease: epidemiology, genetics, physiopathology, clinical management and prognosis of lung disease, with the ultimate goal of improving the quality of life of patients with AATD.

One of the initial objectives of EARCO was to build a network of patients' representatives, researchers and clinical investigators, to identify research needs and establish an agenda for AATD research (3). In this sense, the involvement of patients´ representatives and organizations is essential in order to conduct patient centered quality research. To reach this goal, a task force of EARCO developed and conducted two surveys, one for healthcare providers (HCP), and the second for patients and caregivers to better understand the key research needs and barriers to management in the field of AATD. In this report we present the development, results and implications of these surveys that will run the future research lines of EARCO.

METHOD

A working group composed of 6 EARCO members (4 respirologists and 2 patient representatives) from 5 European countries and representatives of the European Lung Foundation (ELF) was established to develop two surveys: one for HCP and another for patients and caregivers (Figure 1).

Healthcare providers survey

From June to August 2018 the working group analysed the research needs indicated in the recent ERS statement on lung disease in AATD (Table 1) (2) and systematically evaluated the literature published after this statement to identify potential new areas of research. After this revision, 180 research questions were drafted and were sent to an advisory group formed by 5 EARCO members for final check. A final list of 164 research questions was defined, divided into 8 research categories (epidemiology and natural course of the disease (n=25); diagnostic and screening (n=16); awareness and education for HCP and for patients , registries (n=13); clinical manifestations (n=23); outcomes and monitoring (n=38); augmentation therapy (n=23); other treatments / AATD therapies (n=8); other non pharmacological interventions (n=18). From the 29th March to May 1st 2019, an online questionnaire was sent to AATD experts around Europe who were asked to grade each research question anonymously using a five-level scale (from 1= unimportant to 5= very important). Time for completion of the questionnaire was estimated to be 20 to 30 minutes. The complete questionnaire is shown in Supplementary material (S1).

Patients' survey

During the same period, a survey for patients and caregivers was developed. The questionnaire was elaborated by the same working group of members of EARCO, including patient representatives, and the representatives of the ELF. The draft was reviewed by an advisory group of 4 expert patients with AATD from 4 European countries, and revised to ensure that it met the needs of the project and would be relevant, interesting and accessible for patients and caregivers.

The survey was provided in 9 languages: English, Dutch, French, German, Italian, Polish, Portuguese, Serbian and Spanish. The survey was online for six weeks during November 2018/January 2019 and promoted through the networks and social media of Alpha-1 Global, Alpha-1 patient organizations and groups, ELF, ERS and members of the CRC.

After collecting demographic data of the participants, the survey appeared as divided in two parts: A) questions about the most challenging aspects of managing the disease and barriers to treatment and B)

research needs. Patients and caregivers were asked to rate the challenge to manage each aspect of the disease and barriers to treatment (1=Very difficult, 2= Difficult, 3= Not very difficult, 4= Not an issue). Research need questions were divided into 6 categories: symptoms and burden of the disease; areas of research; diagnosis and awareness of the disease; treatment; treatment burden; self-management and education. Participants were asked to rate each research priority question by order of importance (Unimportant, Not very important, Important, Very important, No Opinion). Data are presented as the percentage of responders that rated each item as either important or very important. The complete questionnaire is presented in Supplementary material S2

Statistical analysis

Since the survey was exploratory and there were no a priory hypothesis, no contrasts of hypothesis were performed. Data are presented as descriptive statistics only with mean values or percentages, when appropriate.

RESULTS

Health care professionals' survey

The survey was sent electronically to 230 AATD experts in Europe and we received 94 complete questionnaires (response rate 41%) from 24 countries. The majority (76.6%) of the participants in the HCP survey were aged between 40 and 60 years old. Most of responders (58.5%) had an experience of 5-20 years in following and treating patients with AATD, while 71% visited more than 5 patients with severe deficiency per year. Most of the responders (92.6%) were pulmonologists.

Table 2 shows the 20 most rated research priorities. The top 5 questions identified by HCP were: causes of variable progression and poor outcomes (mean score 4.6/5), improvement of early and accurate diagnosis (4.52), initiation of augmentation therapy (4.51), effectiveness of self-management interventions (4.49), and optimal dose regimen for augmentation therapy (4.38). Other questions considered relevant addressed the definition of fast decliner, severity and impact of exacerbations, and

improvement of awareness. The complete list of responses is shown in the Supplementary material S3.

Patients, family members and caregivers' survey

Characteristics of respondents

A total of 438 questionnaires from 26 countries were completed. 84% were individuals diagnosed with AATD and 16% were parents, relatives or caregivers. Among the individuals diagnosed with AATD, 70% were PI*ZZ. More than half of respondents were diagnosed by a respiratory specialist (56%) with the most likely cause for diagnosis being COPD (32%) followed by family testing (17%). Almost two thirds of respondents were former smokers (62%) (Table 3).

Among the survey responses, 124 (28%) were from people living in one of the following countries where augmentation therapy is currently not reimbursed (Australia, Denmark, Finland, Ireland, Norway, Sweden and United Kingdom) and 239 (55%) from people living in countries where augmentation is reimbursed (Argentina, Austria, France, Germany, Italy, Portugal, Spain, Switzerland and United States of America). Seventy-five questionnaires (17%) were from respondents from countries where reimbursement was only partial or unclear status. The characteristics of the respondents were similar in both groups (Table 3).

Most challenging aspects to manage and barriers for treatment

Figure 2 shows the aspects of the disease considered most challenging by patients and caregivers. Decreased exercise tolerance and shortness of breath were the most difficult aspects identified by patients, followed by not feeling fit or having the strength to do daily activities, tiredness and fatigue.

Among the most challenging aspects/barriers for treatment, the three considered most important were the access issues to augmentation therapy, the professional implications of the diagnosis of AATD and the access to maintenance classes or using fitness centers after rehabilitation for regular exercise (Figure 3).

There were important differences between reimbursed and non-reimbursed countries. Respondents in non-reimbursed countries identified as most challenging barriers for treatment of all aspects related to augmentation therapy: access issues to augmentation therapy in their healthcare system, hospital administration of augmentation therapy, and time consumed in augmentation therapy. In contrast, individuals in reimbursed countries identified as a challenge access to maintenance classes or fitness centers to maintain fitness after rehabilitation; access to pulmonary rehabilitation, and impact of transplant in patients and their families (Figure 3).

Research prioritization by patients and caregivers

Almost the totality of the respondents (99%) considered a priority improving knowledge of AATD, in particular among General Practitioners (GPs). Other top research areas identified were: access to AATD specialized centers (97%); access to reliable, easy to understand information about living with AATD (97%); being able to recognize an exacerbation (97%); targeted screening programs for COPD and asthma patients (96%); and having an action plan for exacerbations and easy access to healthcare during episodes (96%) (Table 4). The complete survey results by section are shown in the Supplementary material S4.

Differences in research prioritization between countries according to reimbursement of therapy

Top research priorities identified by respondents in reimbursed and non-reimbursed countries are shown in Table ~~3~~ 4. For both groups, top research priorities included more evidence on effectiveness of augmentation therapy, education for physicians on diagnostic techniques, algorithms for treatment and interpretation of results, and improving knowledge of AATD in particular among GPs. Respondents in non-reimbursed countries considered a priority having access to AATD specialized centres and access to reliable, easy to understand information about AATD, and having an action plan for exacerbations. For individuals in reimbursed countries, a personalized integrated care plan including physical activity, targeted screening programs for COPD and asthma patients, or being able to recognize an exacerbation were also relevant, among others. Research on alternatives to

intravenous augmentation therapy was also considered relevant for these participants. The complete survey results by type of country are shown in the Supplementary material S5.

DISCUSSION

International collaboration is crucial to develop strategies for improvement of patient care and research in the field of rare diseases. Although research in AATD has been conducted for more than 50 years (5), there are still several areas of uncertainty. On one side the limited number of patients affected with the disease, which is a hurdle for large epidemiological studies (6) or sufficiently powered clinical trials (7), and, on the other side, the reduced investment in research in rare diseases in general. Both of these challenges represent a motivation to join forces and direct research to the aspects that are considered more relevant by researchers but, more importantly, by the patients themselves.

In this context, the European Respiratory Society (ERS) endorsed the creation of the European Alpha-1 Clinical Research Collaboration (EARCO) (3,4), aimed to establish a collaborative effort to advance understanding through research and improving the quality of life of patients with the disease. The first objective of EARCO was to design and implement a prospective, international registry of patients with AATD in order to understand better the natural history and investigate the impact of different therapies, including augmentation therapy, on the course of the disease (8). This registry is already open and recruiting (information available at https://www.earco.eu/registry/). But beyond the registry, or in addition to it, EARCO wants to establish a research agenda for AATD and, in order to develop this agenda, a working group designed and conducted the current survey of unmet needs and challenging aspects to management and research in AATD for HCPs and patients.

Healthcare providers' research priorities

The main research priorities for HCPs were focused on the understanding of the evolution of the disease and the risk factors for poor outcomes and, consequently, the identification of the best candidates, the best regimens and the right time to initiate augmentation therapy. The first prospective studies of cohorts of patients with AATD indicated the large variability in rates of decline of lung

function, in particular between index and non-index cases and between smokers and never smokers (9,10). However, these factors do not completely explain the variability in the natural history of lung disease in AATD (11,12). Although individual cases may have a poor evolution, it is recognized that the majority of never smoker, non-index cases with AATD have the same survival as the general population and therefore may not require any specific treatment (13); but early identification of at-risk individuals is crucial because the treatment only slows down the evolution of emphysema, but does not restore the damaged lung (14).

Indications and regimens of administration of augmentation therapy have remained unchanged for more than 30 years (15), but evidence has accumulated suggesting that the needs for treatment may be different for different patients (16). Only recently, the biochemical efficacy of double doses of AAT has been tested in a pilot study (17) and a clinical trial comparing different doses is ongoing (18); and different routes of administration, such as inhaled AAT, have also been explored (19). It is clear that more research is needed on identifying the right patient and the right therapeutic regimen in a more personalised approach to augmentation therapy (16). Interestingly, these research priorities identified match very well with those proposed by the ERS task force on AATD (2) (Table 1)

Other research priorities that were selected by both HCPs and patients were the need of early and accurate diagnosis and the design of targeted screening programs. Since both lung and liver AATD-associated diseases are irreversible, early identification is crucial to stop the evolution of the disease at mild initial stages (20,21). Studies conducted in the 90's showed that, on average, patients with AATD had a delay in diagnosis of around 8 years and more than 20% of patients had visited four or more physicians before the diagnosis was established (22). Moreover, this finding refers to those who were diagnosed, but epidemiological studies have indicated that despite several information campaigns and detection programs, the majority of patients remain undiagnosed and do not receive appropriate care (1,6). Therefore, it is not surprising that early diagnosis and the development of effective screening programs were selected as top priorities by patients and HCPs.

Patients and caregivers' research priorities

Dissemination of information about the disease is a necessary first step to improve early and accurate diagnosis of AATD. One of the first priorities by patients was the improvement of knowledge about AATD among GPs. Different surveys in European countries have demonstrated the gaps in knowledge about AATD among different specialists, and in particular among GPs (23,24). This is relevant, because in many countries GPs attend the majority of patients with COPD and they are the first contact of these patients with the health system; therefore, if early diagnosis is the goal, improving knowledge and awareness among GPs must be a priority action.

One of the top priorities for patients and caregivers was the access to specialized, reference centers for care of AATD. Due to its low prevalence, it is almost impossible for a single clinician or department to accumulate enough expertise in diagnosis and management of the disease; therefore, the care for patients with AATD is best organised in reference centres that can provide the highest standard of care and advice to the individuals affected and their families whilst also contributing to knowledge accumulation. This is in line with the recommendations of the European Commission about management of rare diseases (25). The recent ERS statement on AATD included a description of the optimised format of service provision by a reference center for AATD (2). These reference centres must establish a registry of their activity and collect information of the natural history of the patients prospectively. The development of registries is crucial as the only way for the successful accumulation of knowledge about the clinical characteristics, evolution, natural history and response to treatment of patients with rare diseases, such as AATD.

The next priority for patients was access to reliable information. In an era of misleading information it is very relevant for patients to be able to identify reliable sources of medical information, such as information from scientific societies and the patient's associations. Examples of reliable produces of patient information and support for the AATD community are the European Lung Foundation (https://www.europeanlung.org), Alpha-1 Global (www.alpha1-global.org) , the Alpha-1 Foundation (https://www.alpha1.org), and several national Alpha-1 patients' associations, including the Alpha-1 UK Support Group (www.alpha1.org.uk) and Alpha1 Deutschland (www.alpha1-detschland.org), among others.

Finally, among the top priorities for patients we found the need to recognise an exacerbation and some aspects related to exercise and rehabilitation. These are medical aspects related to self-management, that can potentially improve the quality of life of the patients, but, interestingly, they were ranked just below some other organisational aspects of the disease.

Challenging aspects to manage for patients and barriers for treatment

Patients identified problems related with decreased exercise tolerance and shortness of breath as the most difficult to manage, followed by other similar concepts such as tiredness and fatigue. Other respiratory symptoms, such as cough or even exacerbations, were not perceived as so difficult to manage. This is related with the perception that the access to pulmonary rehabilitation or to maintenance classes of exercise or access to fitness centers were amongst the most challenging barriers for treatment mentioned by patients. Strategies to provide adequate access to pulmonary rehabilitation and for maintaining adequate levels of physical activity must be encouraged.

Professional implications and additional costs due to the disease or the therapy were also very high in the ranking of barriers for treatment. Patients with lung disease associated with AATD are younger than patients with usual COPD and in most cases professionally active, and therefore the disease may have a huge impact in their professional lives and economic status.

Differences between patients living in countries where augmentation is reimbursed or not

The ERS statement on AATD (2) highlighted the differences in access to specialized care and specific treatments for patients in Europe. Regarding augmentation therapy, there are inequalities of access in different European countries (25,26), which were confirmed in a recent European survey (27); but even in countries where augmentation is available and reimbursed there are differences in prescribing habits between regions, cities and even centers in the same city depending on personal views of attending physicians about efficacy of treatment (27). These differences in access to treatment have an impact beyond the direct effect of therapy. In our survey we have observed worse scores in all challenging aspects of management in patients living in countries where augmentation is not reimbursed. It is likely that patients living in countries where augmentation is reimbursed may have

more frequent contact with HCPs and better knowledge about their disease. This is a new and unexpected finding of our survey that requires corrective actions in countries without augmentation therapy available.

Not surprisingly, the most challenging barrier for treatment for patients in non-reimbursed countries was, by far, the access issues to augmentation therapy, while patients in reimbursed countries indicated the maintenance of physical activity as the most challenging barrier for treatment. Again, in the majority of items, patients in non-reimbursed countries scored lower (worse) than patients in reimbursed countries.

Conclusions

The main research and management priorities identified by HCPs and patients included:

1. Markers of prognosis of the disease. Understanding the natural history of AATD.

2. Personalising treatment: When? Which regimen? To whom?

3. Improve information to physicians, including GPs, and improve early and accurate diagnosis

4. Access to specialised, reference centers and access to reliable information for patients

5. Equal opportunities for access to existing therapies: augmentation, pulmonary rehabilitation and maintenance of physical activity.

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Table 1. Research priorities identified by the ERS task force on pulmonary disease in alpha-1 antitrypsin deficiency (ref. 2)

1. Biomarkers of emphysema progression in AATD

2. Biomarkers of response to augmentation therapy

3. Research on the minimum clinically important difference (MCID) in rate of decline in lung density

4. Personalised augmentation therapy, with individualised selection of therapeutic regimen according to the patient needs

5. Development of genetic and regenerative therapies

6. Other types of treatment, such as biochemical inhibitors of neutrophil proteinases.

7. Development of specific patient-reported outcomes (PROs) for patients with emphysema associated with AATD.

8. Efficacy of augmentation therapy after lung transplant in AATD patients

Table 2. Most rated research questions by respiratory specialists.

Research question	Score
What are the causes of fast progression and poor outcome in patients with AATD?	4.60
How can we improve early and accurate diagnosis in AATD?	4.52
When should augmentation therapy be initiated?	4.51
Are self management interventions effective in AATD patients?	4.49
What is the optimal dose regimen (dose and frequency of administration) of augmentation therapy?	4.38
What is the clinically valid definition of fast decliner, what is advisable observation period?	4.33
How should the severity of an exacerbation, in AATD patients, be assessed and what is its impact on long-term outcomes?	4.31
How can awareness of AATD, among physicians, be improved?	4.27
What is the prevalence of emphysema among never smokers PiZZ?	4.27
What is the impact that the delay of diagnosis has in the prognosis of the disease?	4.25
What are the risk factors, other than cigarette smoking, for the development of lung disease in AATD?	4.25
How can delay in diagnosis be reduced?	4.24
Does an early referral to a specialist in AATD change outcome in patients?	4.24
Which are the best lung function tests for the follow-up of pulmonary disease in AATD patients?	4.23
What is the relation between bronchiectasis and AATD?	4.20
What is the most appropriate AAT blood concentration to consider severe and intermediate AATD?	4.19
Could augmentation therapy be effective in other phenotypes/genotypes with low levels such as SZ?	4.19
Should the laboratory diagnosis algorithm be standardized in Europe?	4.18
What is the therapeutic efficacy of aerosol AAT preparation?	4.18
What is the role of augmentation therapy for reduction of exacerbations frequency and severity?	4.17

Footnote: Scores range from 1=unimportant to 5=very important. Answers are ranked by mean score

Table 3. Patients´demographics and clinical characteristics

Variable	Total N=438	From non-Reimbursed countries (N=124)	From reimbursed countries (N=239)
Patient Parent, relative or caregiver	368 (84) 70 (16)	107 (86) 17 (14)	194 (81) 45 (19)
Age, years; mean	50	54	52
Sex, female	254 (58)	78 (63)	132 (55)
Smoking Active Former	 9 (2) 272 (62)	 4 (3) 78 (66)	 5 (2) 126 (56)
Alcohol	241 (55)	69 (58)	113 (51)
Environmental exposure	127 (29)	36 (30)	69 (31)
Lung transplant recipient	18 (4)	1 (1)	3 (1)
Liver transplant recipient	5 (1)	2 (2)	3 (1)
Diagnosis made by: Pulmonologist GP Gastro/Hepatologist Pediatrician Other	 245 (56) 79 (18) 31 (7) 26 (6) 61 (14)	 56 (47) 38 (32) 7 (6) 5 (4) 13 (11)	 125 (58) 29 (14) 19 (9) 14 (7) 27 (12)
Reason for diagnosis: COPD Family testing Asthma Liver disease Panniculitis Other	 140 (32) 74 (17) 39 (9) 26 (6) 4 (1) 153 (35)	 31 (26) 25 (21) 14 (12) 7 (6) 2 (2) 41 (33)	 68 (30) 45 (20) 19 (8) 19 (8) 5 (2) 76 (32)
AATD phenotype ZZ SZ MZ MS Don’t know Other	 306 (70) 39 (9) 44 (10) 4 (1) 26 (6) 18 (4)	 75 (63) 16 (13) 7 (6) 2 (2) 16 (13) 4 (3)	 161 (72) 19 (8) 31 (13) 2 (1) 2 (1) 12 (5)
Mean time since diagnosis, years	12	10	11

Footnote: There were 75 participants from countries with partial reimbursement, not included in any of the two subgroups. All values are n (%), unless otherwise specified.

Table 4 Most important research areas rated by patients and caregivers.

Research area	**% total**	**% non-reimbursed countries**	**% reimbursed countries**
Improving knowledge AATD, in particular among general practitioners	99	99	99
Access to AATD specialised centres	97	99	96
Access to reliable, easy to understand information about living with AATD	97	99	96
Being able to recognise an exacerbation	97	98	97
Targeted screening programs: COPD and asthma patients	96	94	99
Having an action plan for exacerbations and easy access to healthcare during episodes	96	99	95
A personalised integrated care plan including therapeutic physical activity	95	91	98
Education for physicians on diagnostic techniques, algorithm, interpretation of results	95	95	97
Regular communication between healthcare professional team and AATD patient	94	94	97
Having access to pulmonary rehabilitation and being taught the techniques and how to use the equipment at home	93	95	93
Diagnosis in liver disease patients (children and adults)	93	92	95
Educational programs regarding regional/national resources to diagnose and refer AATD patients	93	96	95
Smoking cessation	93	88	96
Develop better ways of teaching people to use their medicines e.g inhalers, oxygen	92	90	94
Diagnosis of non-respiratory diseases associated with AATD	91	90	95
Develop other aspects of integral care (e.g. physical activity, care-giver support, maintaining work or schooling, nutrition, psychological care, sex-life, daily life)	91	85	94
Role of pulmonary rehabilitation	91	89	95
Availability of organ (lung and/or liver) donation	90	91	92
Role of nutrition	90	91	93
Use of vaccines to prevent exacerbations	90	93	90
Relationship between AATD and other diseases	90	94	89
More evidence on effectiveness of augmentation therapy	90	94	92
Different evolution of the disease among patients	89	91	91
Synthetic AAT production to cover the demand	89	91	88
Evidence on the effect of augmentation therapy on reducing exacerbations	89	92	90
Development of an international AATD registry	89	91	89
Alternatives to IV augmentation therapy (e.g. inhaled augmentation therapy)	89	89	94

Footnote: Percentage corresponds to participants that considered each item as important or very important

FIGURES

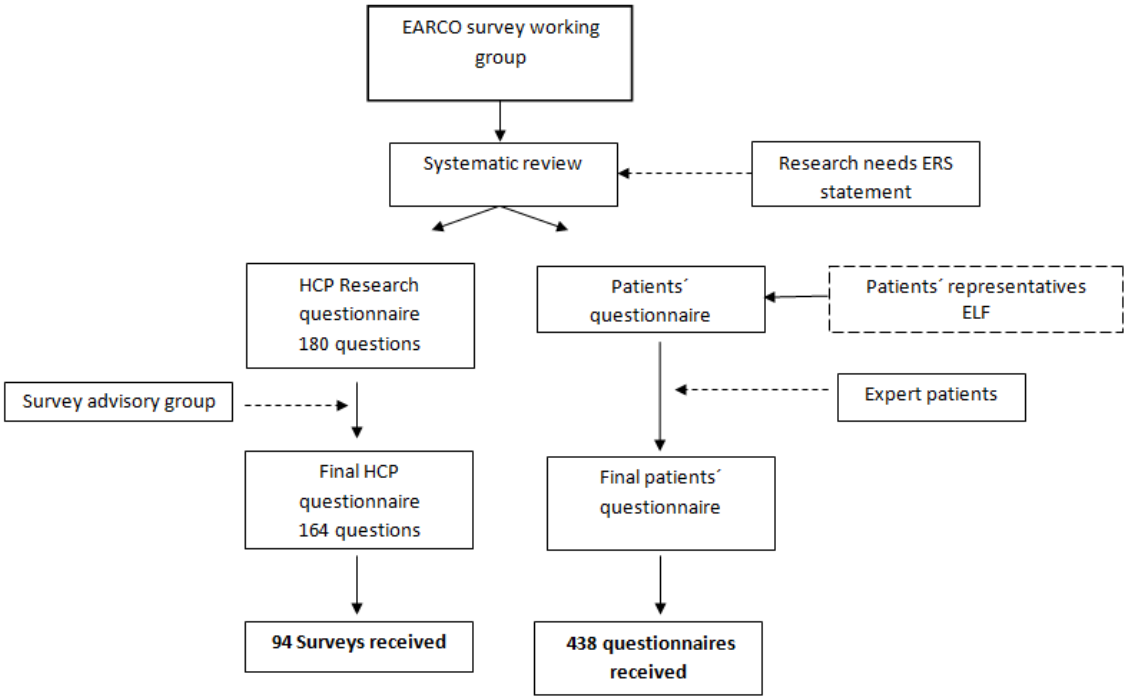
Figure 1. Development of the HCP and patients and caregivers surveys by the EARCO survey working group.

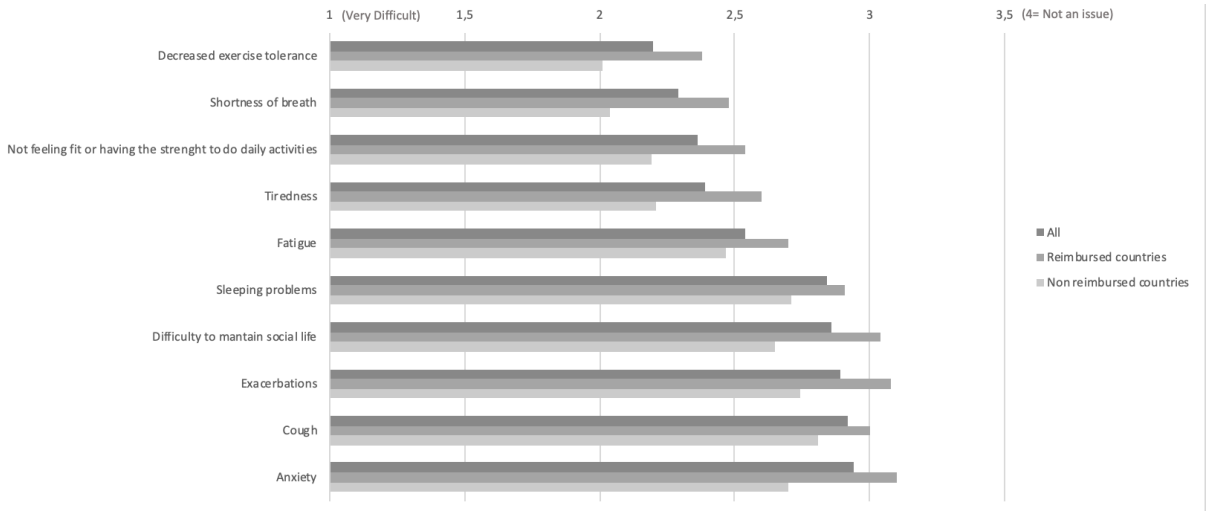
Figure 2. Most challenging aspects to manage for patients.

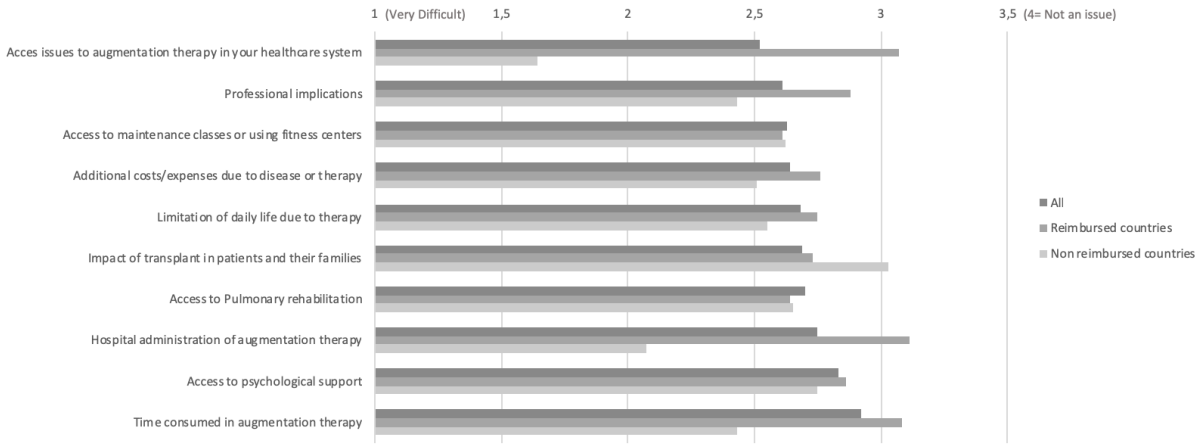
Footnote: The scale used is 1=Very difficult, 2= Difficult, 3= Not very difficult, 4= Not an issue

Figure 3. Most challenging aspects/barriers for treatment

Footnote: The scale used is 1=Very difficult, 2= Difficult, 3= Not very difficult, 4= Not an issue


EARCO survey working group
Systematic review
Research needs ERS statement
HCP Research questionnaire 180 questions
Patients´ questionnaire
Patients´ representatives ELF
Survey advisory group
Expert patients
Final HCP questionnaire 164 questions
Final patients´ questionnaire
94 Surveys received
438 questionnaires received


1 (Very Difficult)
1,5
2
2,5
3
3,5 (4= Not an issue)
Decreased exercise tolerance
Shortness of breath
Not feeling fit or having the strenght to do daily activities
Tiredness
Fatigue
Sleeping problems
Difficulty to mantain social life
Exacerbations
Cough
Anxiety
All
Reimbursed countries
Non reimbursed countries


1 (Very Difficult)
1,5
2
2,5
3
3,5 (4= Not an issue)
Acces issues to augmentation therapy in your healthcare system
Professional implications
Access to maintenance classes or using fitness centers
Additional costs/expenses due to disease or therapy
Limitation of daily life due to therapy
Impact of transplant in patients and their families
Access to Pulmonary rehabilitation
Hospital administration of augmentation therapy
Access to psychological support
Time consumed in augmentation therapy
All
Reimbursed countries
Non reimbursed countries

HCP SURVEY (164 Q)

A. Epidemiology

1. What is the prevalence of liver disease in AATD for the different protein phenotypes/genotypes?
2. What is the prevalence of lung disease in never smoker MZ individuals?
3. What is the prevalence of lung disease in smoker or ex smoker MZ individuals?
4. What are the general healthcare costs related to AATD?
5. What are the healthcare costs related to augmentation therapy in AATD?
6. What are the healthcare costs related to lung disease in AATD?
7. Who manages patients with AATD across Europe, including pulmonologists, gastroenterologists, internal medicine specialists, pediatricians or general practitioners?
8. What is the real prevalence of rare AAT deficient variants?
9. Are the rare AAT deficient variants more frequent in those countries in which the gene frequency of PiZ is lower?
10. What is the real frequency and type of bronchiectasis in AATD?
11. What is the prevalence of emphysema among never smokers PiZZ?
12. What is the prevalence of coexistent lung and liver disease among AATD individuals?
13. What is the prevalence of liver disease in MMalton individuals?
14. What is the prevalence of other less frequent manifestations, such as panniculitis?
15. How many children with liver diseases have lung and or liver problems later in life?
16. Do children without signs of liver problems develop lung/liver problems just as often later?
17. What are the criteria to consider the rare/ultra-rare SERPINA1 aberration as clinically important?
18. What is the prevalence of patients referred to lung or liver transplant; how many of them actually receive a transplant?
19. What is the survival of AATD patients receiving a lung transplant?
20. How many patients receive surgical or endoscopic LVR?
21. What is the prevalence of never smokers PiZZ without lung disease?

B. Diagnostic and screening

1. Would it be useful to include AAT in the current newborn screening program?
2. Who are the family members of a patient PI*ZZ that should be screened for AATD?
3. Who are the family members of a patient PI*MZ that should be screened for AATD?
4. Who are the family members of a patient PI*SZ that should be screened for AATD?
5. What is the laboratory algorithm that should be used for family screening?
6. When should genetic counseling be offered to AATD patients?
7. What are the mechanisms involved in the initiation, maintenance, and hereditability of the epigenetic changes observed in AATD?
8. Should the laboratory diagnosis algorithm be standardized in Europe?
9. What is the role of European certified laboratories for AATD diagnosis?

10. How can we improve early and accurate diagnosis in AATD?
11. What is the role of the lung microbiome in the pathogenesis of AATD?
12. What is the influence of race, sex and socioeconomic status on the natural history and pathobiology of AATD?
13. What is the psycological effect that the diagnosis might have in asymptomatic individuals?
14. What is the psychological burden of childhood diagnosis for parents and during the individuals development?
15. How relevant are the economic implications after diagnosis for asymptomatic individuals? (health insurance, work environment…)
16. What is the best approach to genetic testing considering the potential negative impacts for AATD patients?
17. What is the role that the electronic cigarrete might have in the development of lung disease in AATD?
18. What is the role that pollution might have in the development of lung disease in AATD?
19. What is the role that work exposures might have in the development of lung disease in AATD?
20. Is there a relation between AATD and cystic fibrosis?
21. How can delay in diagnosis be reduced?
22. Should the AAT activity testing be a part of standard diagnostic algorithm for rare SERPINA 1 mutations?
23. What is the impact that the delay of diagnosis has in the prognosis of the disease?

C. **Awareness and education for HCP and for patients. Registries**

1. How can awareness of AATD, among physicians, be improved?
2. How can awareness of AATD in community care services be improved?
3. How can awareness, and use of peer support forums and social media to exchange information about AATD, be raised?
4. How can we improve communication/quality information from HCP to AATD patients?
5. How can patients have and use equipment at home to monitor their symptoms?
6. How can we improve transition from pediatrics to adult care in AATD patients diagnosed during childhood?
7. What is the awareness of pediatricians regarding AATD manifestations in adult life and how can we improve it?
8. What is the awareness of respiratory specialists regarding non-COPD AATD manifestations (including respiratory) in adults and how can we improve it?
9. What is the level of satisfaction that AATD patients have regarding management and research of AATD within the medical community?
10. Should MZ individuals be included in AATD registries?
11. Should individuals with rare mutations be included in AATD registries?

12. Should Alpha1 guidelines be established for all countries that prescribe testing of Alpha1 in case of COPD, asthma and other indications, or is the European guideline sufficient?
13. What is the awareness of pediatricians regarding AATD manifestations in childhood?

D. **Clinical manifestations**

1. What is the relation between asthma and AATD?
2. Does an early referral to a specialist in AATD change outcome in patients?
3. What is the relation between bronchiectasis and AATD?
4. What is the relation between aneurisms and AATD?
5. What is the relation between AATD and cardiac comorbidities such as cardiac disfunction and aortic dissection?
6. What is the relation between cancer and AATD?
7. What is the relation between fibromyalgia and AATD?
8. What are the causes of fast progression and poor outcome in patients with AATD?
9. How should the severity of an exacerbation, in AATD patients, be assessed and what is its impact on long-term outcomes?
10. Are influenza and/or pneumococcal vaccines effective in preventing exacerbations in patients with AATD?
11. Should influenza and/or pneumococcal vaccines be prescribed to asymptomatic heterozygote patients?
12. What is the efficacy and advisability of vaccination against hepatitis B in AATD patients?
13. Are there pulmonary manifestations in children with AATD?
14. What is the most appropriate AAT blood concentration to consider severe and intermediate AATD?
15. What are the triggers for an exacerbation in AATD patients?
16. What is the relation between AATD and exacerbations?
17. What is the relevance that impaired AAT activity might have in the development of lung disease?
18. Is the prevalence of ACO in AATD the same as in COPD?
19. Do we need the pan-European detailed clinical SOP for AATD patients follow-up? How different would it be for healthy AATDs (PiZZ) or PiMZ patients with COPD?
20. In which proportion does AAT increase during inflammation?
21. What is the relation between p-ANCA vasculitis and AATD?

E. **Outcomes and Monitoring**

1. Should MZ individuals without disease manifestations be followed in a respiratory clinic?
2. How often and for how long should MZ without disease be followed in respiratory clinics?
3. Should SZ individuals without disease manifestations be followed in a respiratory clinic?

4. How often and for how long should SZ without disease be followed in respiratory clinics?
5. Should Mnull individuals without disease manifestations be followed in a respiratory clinic?
6. How often and for how long should Mnull without disease be followed in respiratory clinics?
7. Should Mrare individuals without disease manifestations be followed in a respiratory clinic?
8. How often and for how long should Mrare without disease be followed in respiratory clinics?
9. Which are the best blood markers for the diagnosis and follow-up of liver disease in AATD patients?
10. How frequently should AATD patients undergo a transient elastography for the screening of liver disease?
11. Which are the best lung function tests for the follow-up of pulmonary disease in AATD patients?
12. How often should spirometry be performed during follow-up?
13. How often DLCO should be performed during follow-up?
14. How often a lung CT scan should be performed during follow-up?
15. Do specific patient education packages, self-management plans and patients support groups improve outcomes in patients with AATD?
16. What is the role of pulmonary rehabilitation in patients with AATD?
17. Are current PRO used in COPD suitable for AATD individuals?
18. What are the risk factors, other than cigarette smoking, for the development of lung disease in AATD?
19. What are the risk factors, other than alcohol, for the development of liver disease in AATD?
20. What is the best score to evaluate radiology severity and progression in patients with AATD?
21. How often should lung density be measured during follow up in AATD?
22. Is FeNO useful during follow-up in AATD?
23. How can patients at increase risk of poor outcome or needing urgent treatment be identified?
24. What is the correct threshold of AAT serum level for detecting heterozygous carriers?
25. What is the best health status questionnaire to evaluate AATD patients?
26. What is the best prognostic score in AATD?
27. Which index or indices best stratify AATD patients for the purpose of determining disease severity or recommending treatment?
28. Are there CT findings associated with clinically significant features and differential responses to treatment in AATD?
29. Which outcomes matter most to patients and, therefore, are truly patient-centered outcomes in AATD?
30. What is the optimal CT protocol and quantification method in AATD patients?
31. How often and for how long should deficient individuals without clinical manifestations be followed?
32. What is the role of lung transplant in patients with AATD?

33. Should we follow patients with AATD without lung disease after a liver transplant and for how long?
34. What is the average lung function decline for MZ, SZ and SS patients?
35. How is the microbiome in AATD patients, and it is different among phenotypes and compared to non AATD COPD?
36. What is the impact that viral infections have on the evolution of AATD?
37. What is the role of gene therapy in AATD?
38. What is the clinically valid definition of fast decliner, what is advisable observation period?

F. **Augmentation therapy**

1. Could augmentation therapy be effective in other phenotypes/genotypes with low levels such as SZ?
2. Could augmentation therapy be effective in MZ patients?
3. Could augmentation therapy be effective in rare phenotypes/genotypes with normal levels but low AAT enzymatic activity (PiF?)
4. What is the role of AAT augmentation therapy after lung transplantation?
5. What is the role of AAT augmentation therapy after liver transplantation?
6. What is the role of AAT augmentation therapy for panniculitis, in patients with AATD?
7. What is the role of augmentation therapy for fibromyalgia in patients with AATD?
8. What is the optimal dose regimen (dose and frequency of administration) of augmentation therapy?
9. Should augmentation therapy be considered in PI*ZZ patients with bronchiectasis without emphysema?
10. What is the role of augmentation therapy in AATD asthmatic patients?
11. What is the therapeutic efficacy of aerosol AAT preparation?
12. What is the role of augmentation therapy for reduction of exacerbations frequency and severity?
13. What are the principal barriers for unequal reimbursement policies for AAT augmentation therapy across Europe?
14. How can augmentation therapy be accessible to all patients across Europe?
15. What is the real prevalence of adverse effects of augmentation therapy?
16. What is the role of home intravenous augmentation therapy?
17. Are longer regimes (biweekly and every 3 weeks) really equivalent to weekly augmentation therapy?
18. What is the effect of the discontinuation of augmentation therapy during holidays of hospital admissions?
19. Should augmentation therapy be administered in patients with emphysema with preserved spirometry?
20. Should augmentation therapy be administered in a home setting?
21. What are the side effects of augmentation therapy?
22. When should augmentation therapy be initiated?

23. Do PROs improve (deteriote significantly less) under augmentation therapy?

G. **Other treatments/AATD therapies**

1. What is the role of endoscopic therapy in AATD?
2. What is the role of lung volume reduction surgery in AATD?
3. What is the role of systemic steroids during an exacerbation of AATD?
4. What is the role of inhaled steroids in patients with AATD?
5. What is the role of oral mucolytics in patients with AATD?
6. What is the role of long-term antibiotic therapy in AATD patients?
7. What is the role of inhaled antibiotics in patients with AATD and clinical manifestations?
8. What is the role of biologics for the management of AATD?

H. **Other non pharmacological interventions**

1. When should pulmonary rehabilitation be offered/started in AATD patients?
2. What is the role of pulmonary rehabilitation in AATD?
3. What is the role of environmental and workplace avoidance of exposure, for lung disease in AATD patients?
4. What is the role of environmental avoidance of exposure, for liver disease in AATD patients?
5. What are the risk factors that should be avoided in AATD patients with liver disease?
6. What are the healthcare costs of AATD management across Europe?
7. How can communication between healthcare professionals and each patient be optimized to improve self-management?
8. Is disease management plan agreed with the patient?
9. How can access to healthcare professionals improve AATD management and control of the disease?
10. How can respiratory rehabilitation be accessible to all patients across Europe?
11. What is the impact of diagnosis and treatment of comorbidities in AATD patients?
12. Should psychological support be offered to AATD patients?
13. Are self management interventions effective in AATD patients?
14. Should exacerbation action plans be recommended for all AARD patients?
15. Does lung transplant increase survival in AATD patients?
16. How can a patient organisation/self-help group support the patient?
17. How can patient organisations and professionals network better?
18. Is breathing training/physiotherapy useful for patients with AATD?

ELF EUROPEAN LUNG FOUNDATION

Research Priorities in Alpha-1 antitrypsin deficiency (AATD)

Which research topics might have the greatest impact on the lives of people with AATD?

Introduction

We are asking people with Alpha-1 Antitrypsin Deficiency (AATD), or their families and friends, to tell us what we should be looking at to provide answers to the challenges of care, treatment and living with AATD.

The priorities for research identified by people with AATD and their families may be different to the point of view of doctors and researchers. The aim of this survey is to find out which topics of research YOU think are most relevant or most likely to provide answers to the challenges of treating and living with AATD and will therefore have the greatest impact on quality of life for people with AATD.

This survey is part of the scope of work lead by EARCO (European Alpha-1 Research Collaboration), a Clinical Research Collaboration (CRC) of the European Respiratory Society (ERS), to facilitate multidisciplinary collaborative research in AATD (www.ersnet.org/research/earco-european-alpha-1-research-collaboration).

Your answers will influence what research is done by these research centres in the future. The questionnaire is mainly focused on the respiratory burden and lung diagnosis and treatment for AATD.

This survey will take up to 15 minutes to complete and is anonymous. If you would like to receive updates or would like to become more involved in the project, you can enter your email address at the end of the survey. If you would like to do this, you will be directed to a different surveymonkey page. This means that your email address and survey responses are separate, and anonymity is maintained.

Your participation will significantly contribute to the success of this project. This survey will close on the 8 December 2019. Thank you very much for your time and effort!

Dr. Marc Miravitlles and Dr. Timm Greulich - CRC EARCO Chairs

ELF EUROPEAN LUNG FOUNDATION

Research Priorities in Alpha-1 antitrypsin deficiency (AATD)

Which research topics might have the greatest impact on the lives of people with AATD?

Instructions

This questionnaire is divided into parts:-

- Part 1 describes your demographics.
- Part 2 - in this part you will be asked which research areas you think should be prioritised:

- **Symptoms and burden of the disease**
- **Areas of research**
- **Diagnosis and awareness of the disease**
- **Treatment burden**
- **Self-management and education**

You are asked to rate each research priority question by order of importance (Unimportant, Not very important, Important, Very important, No Opinion) and rate the challenge you face to manage each aspect of your disease (Not an issue, Not very difficult, Difficult, Very difficult).

Although every item might be very important, we advise you to answer as objectively as possible (pointing out your priorities) so that we can generate new knowledge with direct impact on your quality of life and clinical care.

Finally, you will be asked if there are any additional research priorities that you consider necessary to include. If so, please propose them in the box provided at the end of each area of research.

This survey can be answered by patients, parents, relatives or caregivers of someone with AATD. If you are answering this survey on behalf of someone else, please provide information concerning the patient opinion.

Thank you very much for your time and effort!

Yours sincerely,

Dr. Marc Miravitlles and Dr. Timm Greulich - CRC EARCO Chairs

Please do not hesitate to contact jeanette.boyd@europeanlung.org if you have any questions related to the survey.

ELF EUROPEAN LUNG FOUNDATION

Research Priorities in Alpha-1 antitrypsin deficiency (AATD)

Which research topics might have the greatest impact on the lives of people with AATD?

About you

If you are completing this on behalf of someone with AATD, please add their details in response to the demographic questions

* 1. Are you....?

- ○ A person diagnosed with alpha-1 antitrypsin deficiency (AATD)?
- ○ A parent, relative or caregiver of someone with AATD? (please, specify)
- ○ Other? (please, specify)
- ○ Please specify here if you are not a person diagnosed with AATD

2. What age are you (in years)? (if you are answering this survey on behalf of someone else, please provide the age of the person with AATD)

* 3. Are you..? (if you are answering this survey on behalf of someone else, please provide the gender of the person with AATD)

- ○ Male
- ○ Female
- ○ Prefer not to say

* 4. In which country were you born?

* 5. In which country do you currently live?

ELF EUROPEAN LUNG FOUNDATION

Research Priorities in Alpha-1 antitrypsin deficiency (AATD)

Which research topics might have the greatest impact on the lives of people with AATD?

About your AATD

* 6. For how many years have you been diagnosed with AATD?

* 7. What was the reason for your diagnosis?

- ○ COPD
- ○ Asthma
- ○ Liver disease
- ○ Panniculitis
- ○ Family testing
- ○ Other (please specify)

* 8. Are you a ...

- ○ Current smoker
- ○ Former smoker
- ○ Never smoker

9. Do you drink alcohol?

- ○ No
- ○ Yes

If yes, how many litres per week, on average?

* 10. In your professional activities were/are you exposed to gases, fumes or dust?

- ◯ Yes
- ◯ No

* 11. Who diagnosed your AATD?

- ◯ Family physician / General Practitioner (GP)
- ◯ Respiratory specialist
- ◯ Gastroenterologist / Hepatologist
- ◯ Pediatrician
- ◯ Other (please specify)

* 12. What is your AATD phenotype / genotype?

- ◯ ZZ
- ◯ SZ
- ◯ MZ
- ◯ MS
- ◯ Don't know
- ◯ Other (please specify)

* 13. Have you had a lung transplant?

- ◯ Yes
- ◯ No

* 14. Have you had a liver transplant?

- ◯ Yes
- ◯ No

Part 2: Your experience of AATD

Symptoms and burden of the disease

15. What aspects of the disease do you find most challenging and/or difficult to manage (during the past 12 months)?

	Very difficult	Difficult	Not very difficult	Not an issue	N/A
Shortness of breath	○	○	○	○	○
Not feeling fit or having the strength to do daily activities	○	○	○	○	○
Decreased exercise tolerance	○	○	○	○	○
Tiredness	○	○	○	○	○
Cough	○	○	○	○	○
Sputum (mucus from the lungs)	○	○	○	○	○
Wheezing	○	○	○	○	○
Sleeping problems	○	○	○	○	○
Anxiety	○	○	○	○	○
Depression	○	○	○	○	○
Difficulty to maintain social life	○	○	○	○	○
Exacerbations (episodes of increased or change in colour of sputum, shortness of breath and/or fever that lead you to go to the doctor)	○	○	○	○	○
Frequent hospital admissions	○	○	○	○	○

	Very difficult	Difficult	Not very difficult	Not an issue	N/A
Having regular tests or explorations performed (e.g. lung function testing, computed tomography scan, chest x-ray, liver examinations)	○	○	○	○	○
Jaundice (yellowing of your skin and eyes)	○	○	○	○	○
Cholestasis	○	○	○	○	○
Abnormal liver function tests	○	○	○	○	○
Vomiting	○	○	○	○	○
Swelling or pain in your belly/swollen abdomen	○	○	○	○	○
Poor growth/weight loss	○	○	○	○	○
Poor appetite	○	○	○	○	○
Diarrhea	○	○	○	○	○
Itching	○	○	○	○	○
Fatigue	○	○	○	○	○
Panniculitis	○	○	○	○	○

Other: please give ideas not already included here

Part 2: Your experience of AATD

Treatment Burden

16. What aspects and/or barriers for treatment do you find most challenging and difficult to manage?

	Very difficult	Difficult	Not very difficult	Not an issue	N/A
Access issues to augmentation therapy in your healthcare system	○	○	○	○	○
Hospital administration of augmentation therapy	○	○	○	○	○
Time consumed in augmentation therapy	○	○	○	○	○
Access to pulmonary rehabilitation	○	○	○	○	○
Access to maintenance classes or using fitness centers to maintain fitness after rehabilitation	○	○	○	○	○
Use of inhaled and/or nebulized therapy	○	○	○	○	○
Use of oxygen therapy and/or noninvasive ventilation	○	○	○	○	○
Access to psychological support	○	○	○	○	○
Access to support for family planning and family screening	○	○	○	○	○
Professional implications (ie, loss of job due to disease or therapy)	○	○	○	○	○
Additional costs/expenses due to disease or therapy	○	○	○	○	○
Limitation of daily life due to therapy	○	○	○	○	○
Impact of transplant in patients and their families	○	○	○	○	○

Other: please give ideas not already included here

Part 2: Research Prioritisation

Areas of Research

17. The priorities for research identified by people with AATD and their families may be different from the point of view of doctors and researchers. It is important we understand what patients' research priorities are.

How important do you think the following research areas are to improve AATD management?

	Very important	Important	Not very important	Unimportant	No opinion
Development of an international AATD registry	○	○	○	○	○
More evidence on effectiveness of augmentation therapy	○	○	○	○	○
Alternatives to IV augmentation therapy (e.g. inhaled augmentation therapy)	○	○	○	○	○
Evidence on the effect of augmentation therapy on reducing exacerbations	○	○	○	○	○
Synthetic AAT production to cover the demand	○	○	○	○	○
Gene therapy	○	○	○	○	○
Innovative liver therapies	○	○	○	○	○
AATD in heterozygotes (e.g. MZ phenotype): clinical manifestations, indications for augmentation treatment	○	○	○	○	○

	Very important	Important	Not very important	Unimportant	No opinion
Learning more about the natural development of the disease (including liver disease or other clinical conditions related to AATD)	○	○	○	○	○
Different evolution of the disease among patients	○	○	○	○	○
Evolution of patients after lung and/or liver transplant	○	○	○	○	○
Relationship between lung and liver disease	○	○	○	○	○
Relationship between AATD and other diseases (e.g. asthma, bronchiectasis, vasculitis)	○	○	○	○	○
Investigating the effect of pollution, work exposures, second hand smoking, etc, in the development of lung disease	○	○	○	○	○

Other: please give ideas not already included here

Part 2: Research Prioritisation

Diagnosis and awareness of the disease

18. How important do you think it is to improve the following areas for diagnosis and awareness of AATD?

	Very important	Important	Not very important	Unimportant	No opinion
Screening programs in newborns (neonatal screening)	○	○	○	○	○
Screening programs in the general population	○	○	○	○	○
Targeted screening programs: COPD and asthma patients	○	○	○	○	○
Early diagnosis of the disease using innovative online test procedures	○	○	○	○	○
Diagnosis in liver disease patients (children and adults)	○	○	○	○	○
Improving knowledge of AATD, in particular among General Practitioners	○	○	○	○	○
Education for physicians on diagnostic techniques, algorithm and interpretation of the results	○	○	○	○	○
Diagnosis of non-respiratory diseases associated with AATD (e.g. panniculitis, vasculitis, liver disease)	○	○	○	○	○

	Very important	Important	Not very important	Unimportant	No opinion
Educational programs regarding regional/national resources to diagnose and refer AATD patients	○	○	○	○	○
Implications of being diagnosed with a genetic disease (ethical and economic) and its potential negative impact	○	○	○	○	○

Other: please give ideas not already included here

ELF EUROPEAN LUNG FOUNDATION

Research Priorities in Alpha-1 antitrypsin deficiency (AATD)

Which research topics might have the greatest impact on the lives of people with AATD?

Part 2: Research Prioritisation

Treatment

19. How important do you think it is to improve the following areas for AATD treatment?

	Very important	Important	Not very important	Unimportant	No opinion
Dose regimen of augmentation therapy	○	○	○	○	○
Augmentation therapy after lung transplantation	○	○	○	○	○
Augmentation therapy for panniculitis	○	○	○	○	○
Difficulties in accessing augmentation therapy	○	○	○	○	○
Administration of augmentation therapy at home	○	○	○	○	○
Use of augmentation therapy during holidays/prolonged travel	○	○	○	○	○
Side effects of augmentation therapy	○	○	○	○	○
Availability of organ (lung and/or liver) donation	○	○	○	○	○
Development of multidisciplinary centers	○	○	○	○	○
Develop other aspects of integral care (eg physical activity, care-giver support, maintaining work or schooling, nutrition, pyschological care, sex-life, daily- life)	○	○	○	○	○
Smoking cessation	○	○	○	○	○

	Very important	Important	Not very important	Unimportant	No opinion
Alcohol cessation	◯	◯	◯	◯	◯
Role of nutrition	◯	◯	◯	◯	◯
Role of pulmonary rehabilitation	◯	◯	◯	◯	◯
Role of oxygen therapy	◯	◯	◯	◯	◯
Role of noninvasive ventilation	◯	◯	◯	◯	◯
Use of vaccines to prevent exacerbations	◯	◯	◯	◯	◯
Liver disease therapy	◯	◯	◯	◯	◯

Other: please give ideas not already included here

Part 2: Research Prioritisation

Self-management and education

20. Education, technology and self-awareness, known as self-management, can help each person gain greater control over their disease and to improve daily quality of life.

How important do you think the following areas are in improving self-management of AATD?

	Very important	Important	Not very important	Unimportant	No opinion
Being able to recognize an exacerbation	○	○	○	○	○
Having an action plan for exacerbations and easy access to healthcare during episodes	○	○	○	○	○
An app to facilitate disease management and treatment (e.g. activity diary)	○	○	○	○	○
Regular communication between healthcare professional team and each individual with AATD	○	○	○	○	○
Interaction and information exchange within a patient organization or self-help group	○	○	○	○	○
Using peer support forums and social media to exchange information with others	○	○	○	○	○
Having access to reliable, easy to understand information about different aspects of living with AATD	○	○	○	○	○

	Very important	Important	Not very important	Unimportant	No opinion
Develop better ways of teaching people to use their medicines (e.g. inhalers, oxygen)	○	○	○	○	○
A personalized integrated care plan including therapeutic physical activity	○	○	○	○	○
Having access to pulmonary rehabilitation and being taught the techniques and how to use the equipment at home	○	○	○	○	○
Having access to AATD specialized centres	○	○	○	○	○

Other: please give ideas not already included here

ELF EUROPEAN LUNG FOUNDATION

Research Priorities in Alpha-1 antitrypsin deficiency (AATD)

Which research topics might have the greatest impact on the lives of people with AATD?

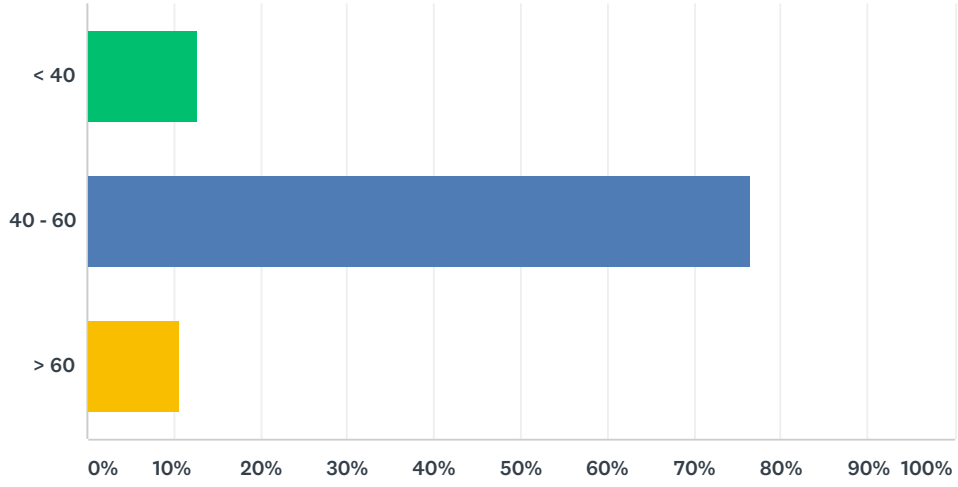
Thank you for completing the AATD patient survey.
Your contribution is greatly appreciated.

If you would like to receive the results of the survey and updates on the project please follow this link to enter your email address: https://www.surveymonkey.co.uk/r/EARCO-ATTD
Please note that the European Lung Foundation will only contact you in relation to this survey and to send you updates about this project. We will not share your email address with any third parties. Your email address will be stored on our secure servers and we will retain your email only for as long as is necessary to provide you with the service stated above.

Please contact Jeanette Boyd at the European Lung Foundation if you have any queries: jeanette.boyd@europeanlung.org

Q1 Indicate your Age range

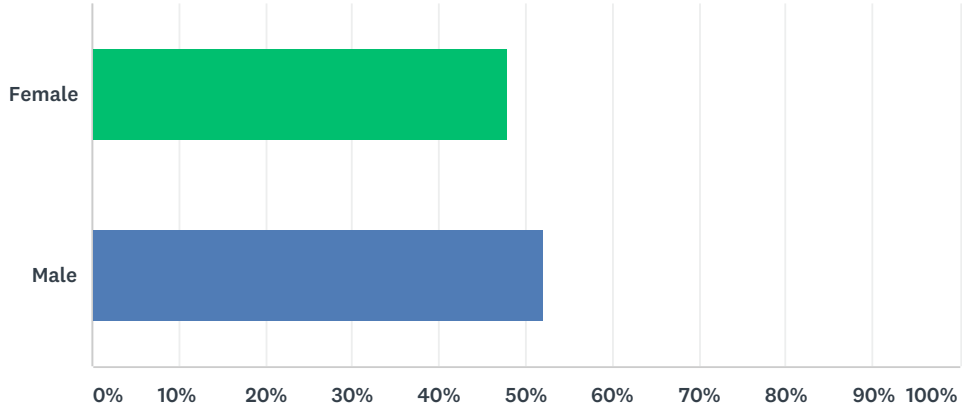
Answered: 94 Skipped: 0



ANSWER CHOICES	RESPONSES	
< 40	12.77%	12
40 - 60	76.60%	72
> 60	10.64%	10
TOTAL		94

Q2 What is your gender?

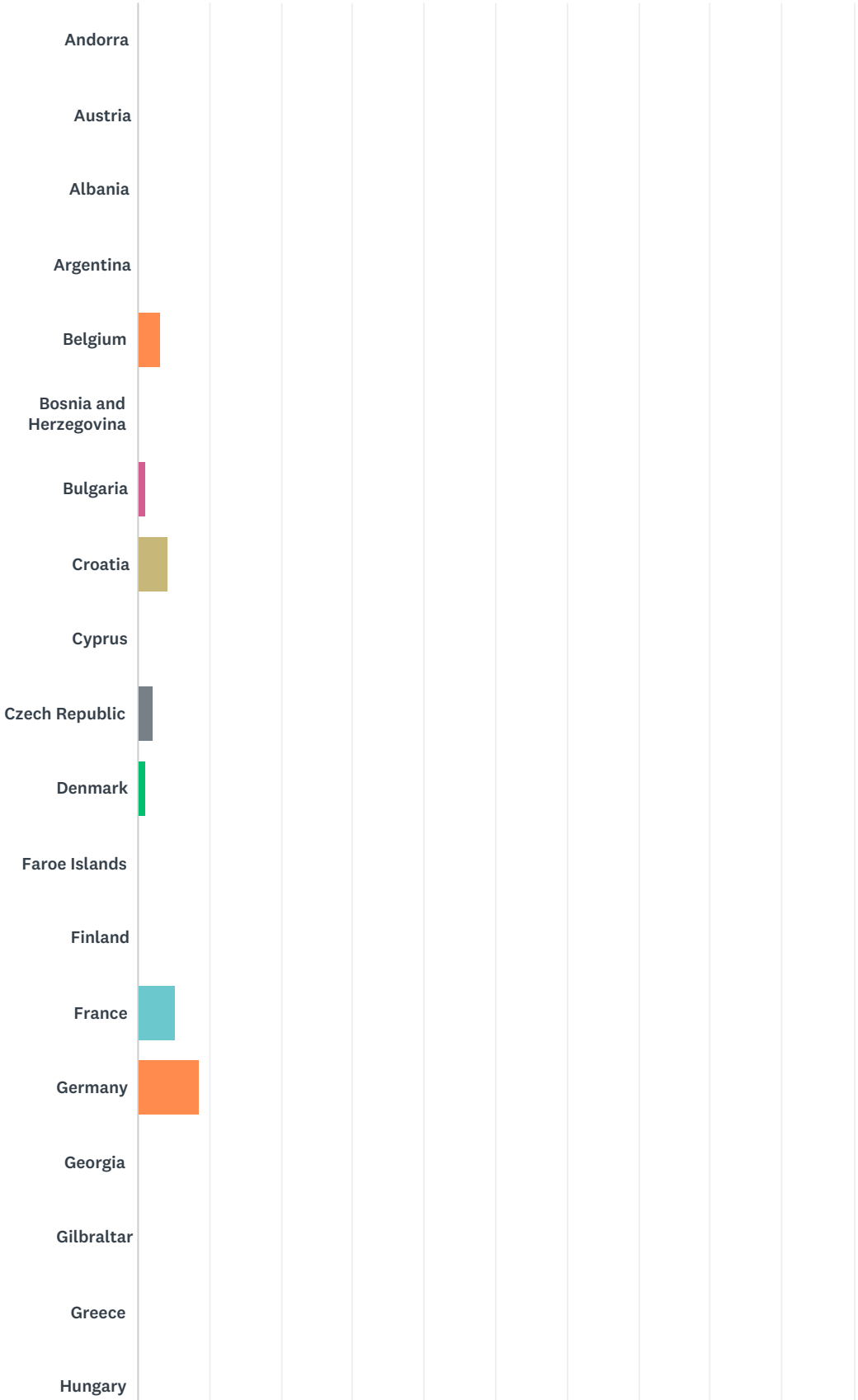
Answered: 94 Skipped: 0

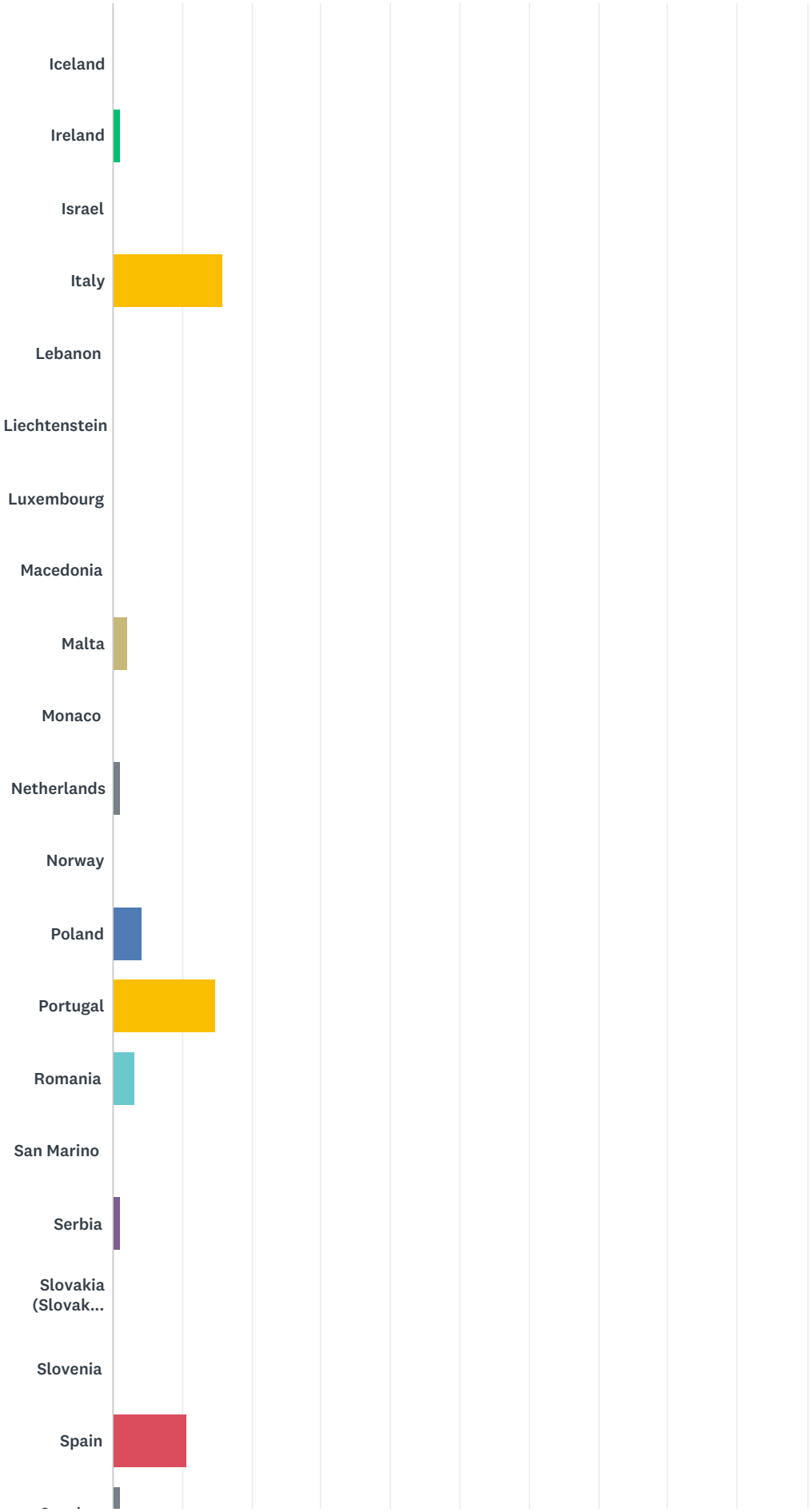


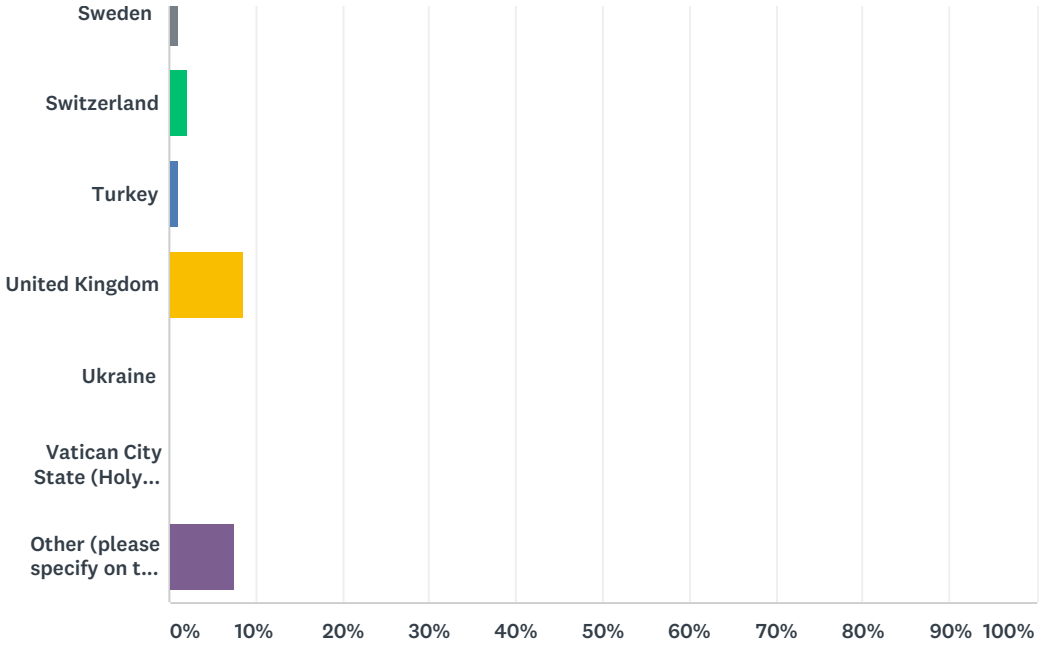
ANSWER CHOICES	RESPONSES	
Female	47.87%	45
Male	52.13%	49
TOTAL		94

Q3 In which country do you currently work?

Answered: 94 Skipped: 0




Iceland
Ireland
Israel
Italy
Lebanon
Liechtenstein
Luxembourg
Macedonia
Malta
Monaco
Netherlands
Norway
Poland
Portugal
Romania
San Marino
Serbia
Slovakia (Slovak...
Slovenia
Spain

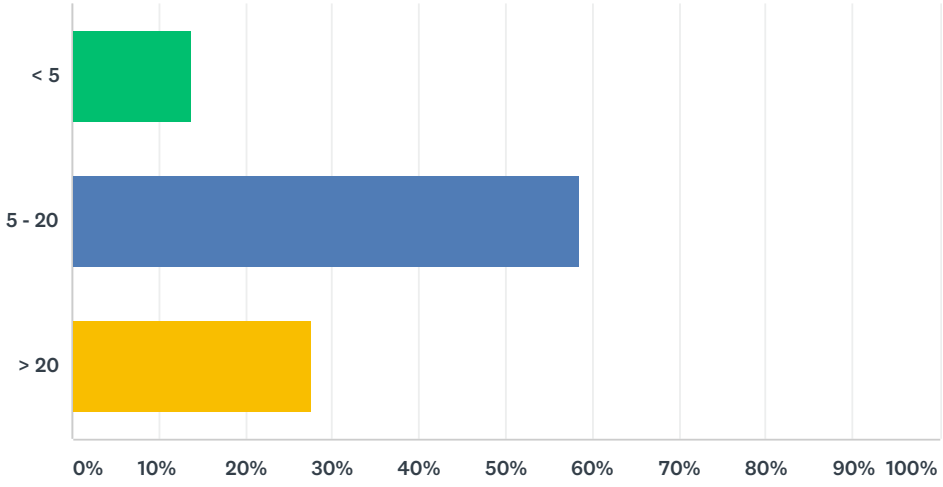


ANSWER CHOICES	RESPONSES	
Andorra	0.00%	0
Austria	0.00%	0
Albania	0.00%	0
Argentina	0.00%	0
Belgium	3.19%	3
Bosnia and Herzegovina	0.00%	0
Bulgaria	1.06%	1
Croatia	4.26%	4
Cyprus	0.00%	0
Czech Republic	2.13%	2
Denmark	1.06%	1
Faroe Islands	0.00%	0
Finland	0.00%	0
France	5.32%	5
Germany	8.51%	8
Georgia	0.00%	0
Gilbraltar	0.00%	0
Greece	0.00%	0
Hungary	0.00%	0
Iceland	0.00%	0
Ireland	1.06%	1

Israel	0.00%	0
Italy	15.96%	15
Lebanon	0.00%	0
Liechtenstein	0.00%	0
Luxembourg	0.00%	0
Macedonia	0.00%	0
Malta	2.13%	2
Monaco	0.00%	0
Netherlands	1.06%	1
Norway	0.00%	0
Poland	4.26%	4
Portugal	14.89%	14
Romania	3.19%	3
San Marino	0.00%	0
Serbia	1.06%	1
Slovakia (Slovak Republic)	0.00%	0
Slovenia	0.00%	0
Spain	10.64%	10
Sweden	1.06%	1
Switzerland	2.13%	2
Turkey	1.06%	1
United Kingdom	8.51%	8
Ukraine	0.00%	0
Vatican City State (Holy See)	0.00%	0
Other (please specify on the comment box)	7.45%	7
TOTAL		94

Q4 Indicate the range of years of Experience in AATD you have:

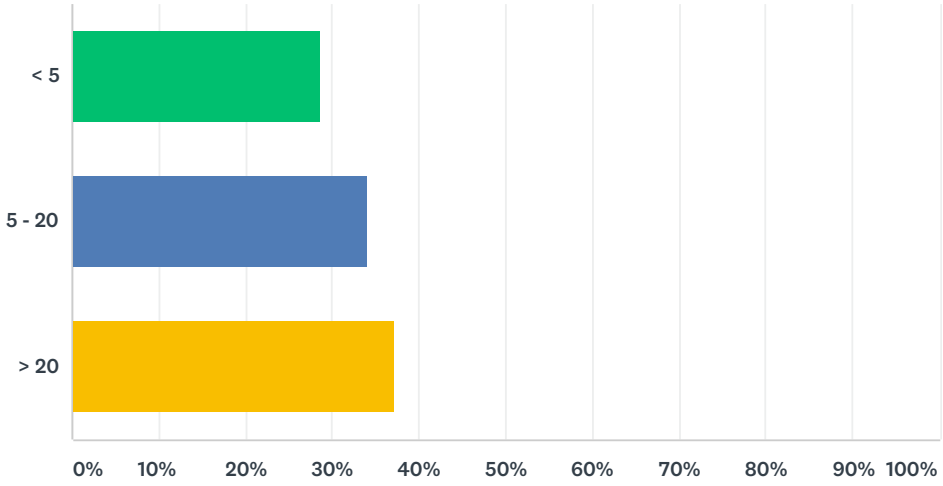
Answered: 94 Skipped: 0



ANSWER CHOICES	RESPONSES	
< 5	13.83%	13
5 - 20	58.51%	55
> 20	27.66%	26
TOTAL		94

Q5 Indicate the average number of patients with severe deficiency (seen per year):

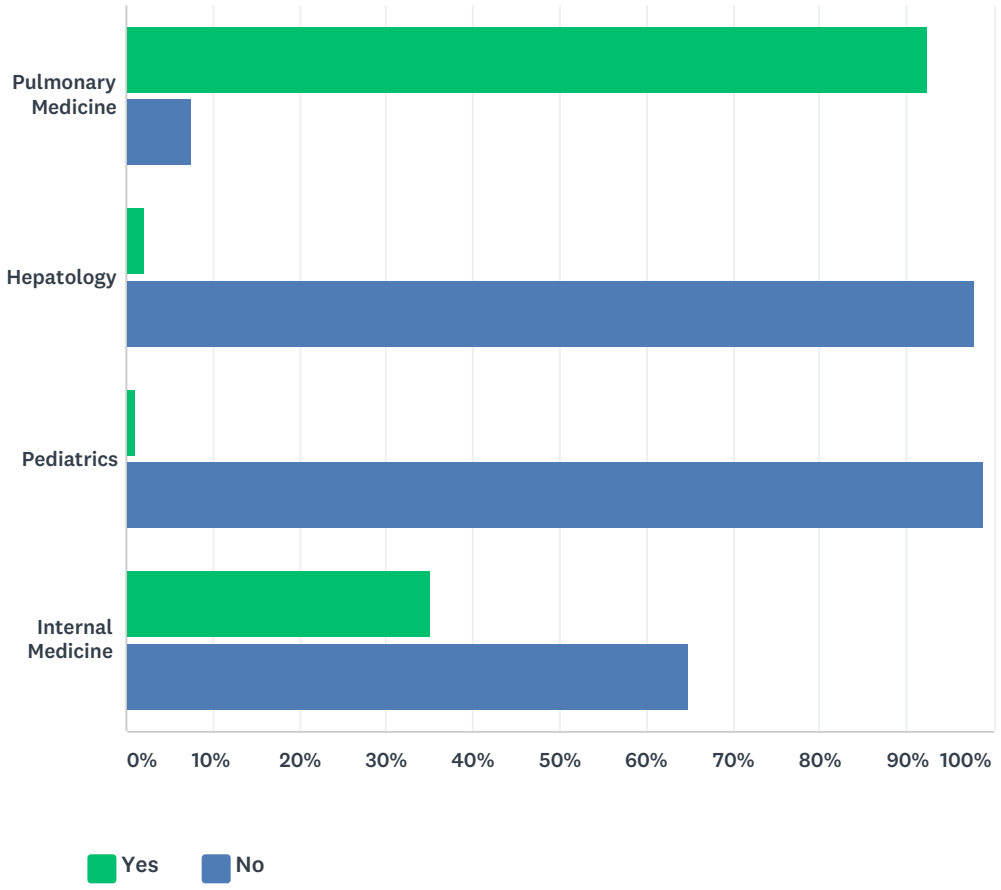
Answered: 94 Skipped: 0



ANSWER CHOICES	RESPONSES	
< 5	28.72%	27
5 - 20	34.04%	32
> 20	37.23%	35
TOTAL		94

Q6 Are you a Specialist in:

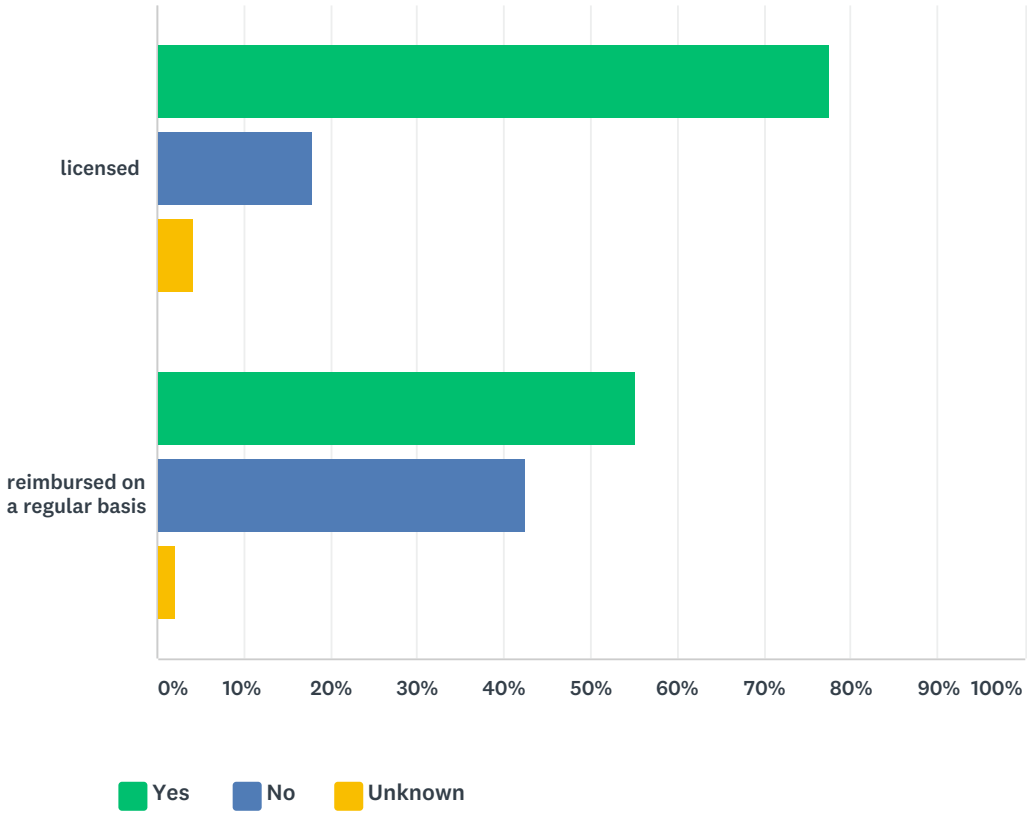
Answered: 94 Skipped: 0



	YES	NO	TOTAL	WEIGHTED AVERAGE
Pulmonary Medicine	92.55% 87	7.45% 7	94	1.07
Hepatology	2.13% 2	97.87% 92	94	1.98
Pediatrics	1.06% 1	98.94% 93	94	1.99
Internal Medicine	35.11% 33	64.89% 61	94	1.65

Q7 Is the Augmentation Therapy in your country:

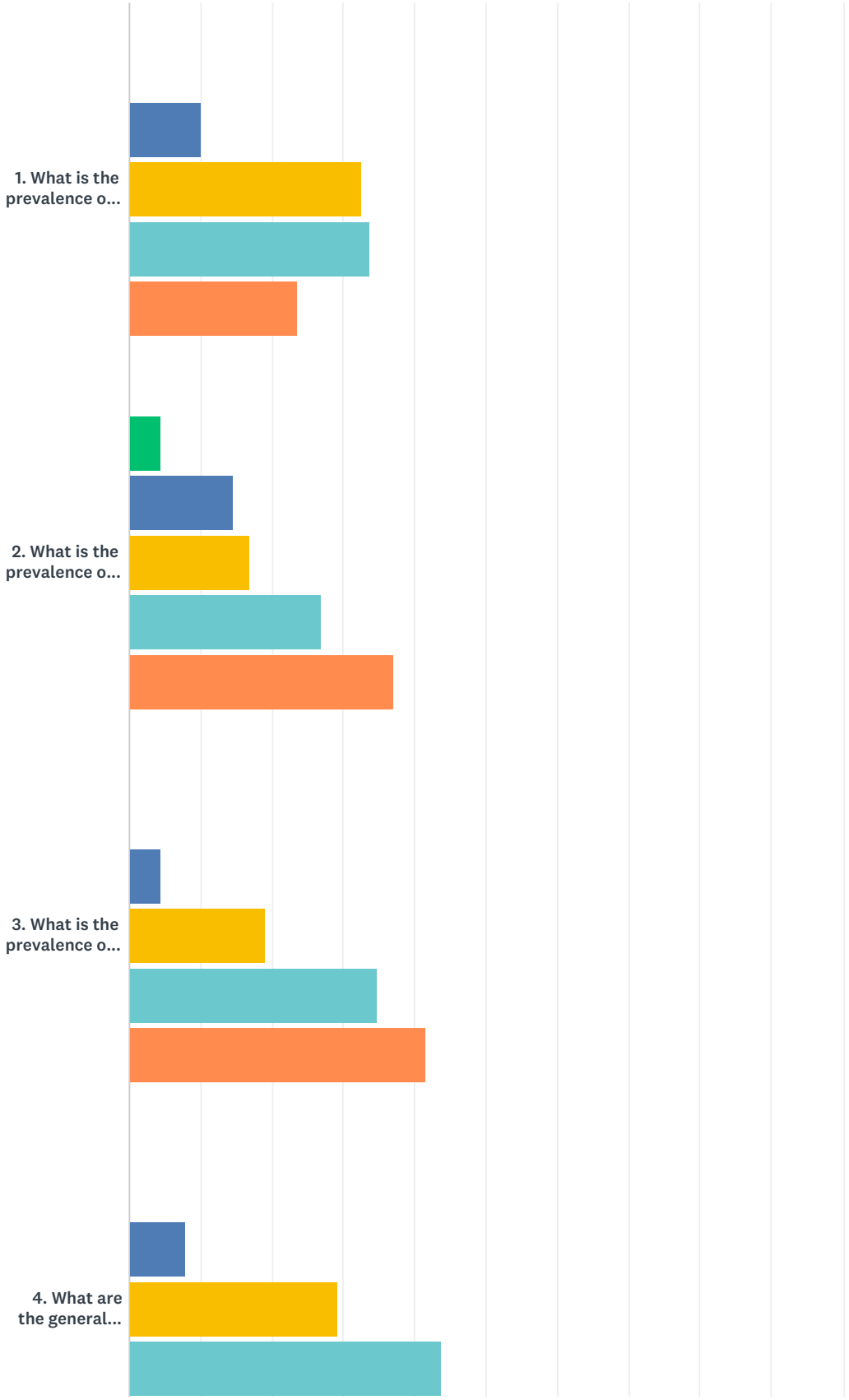
Answered: 94 Skipped: 0

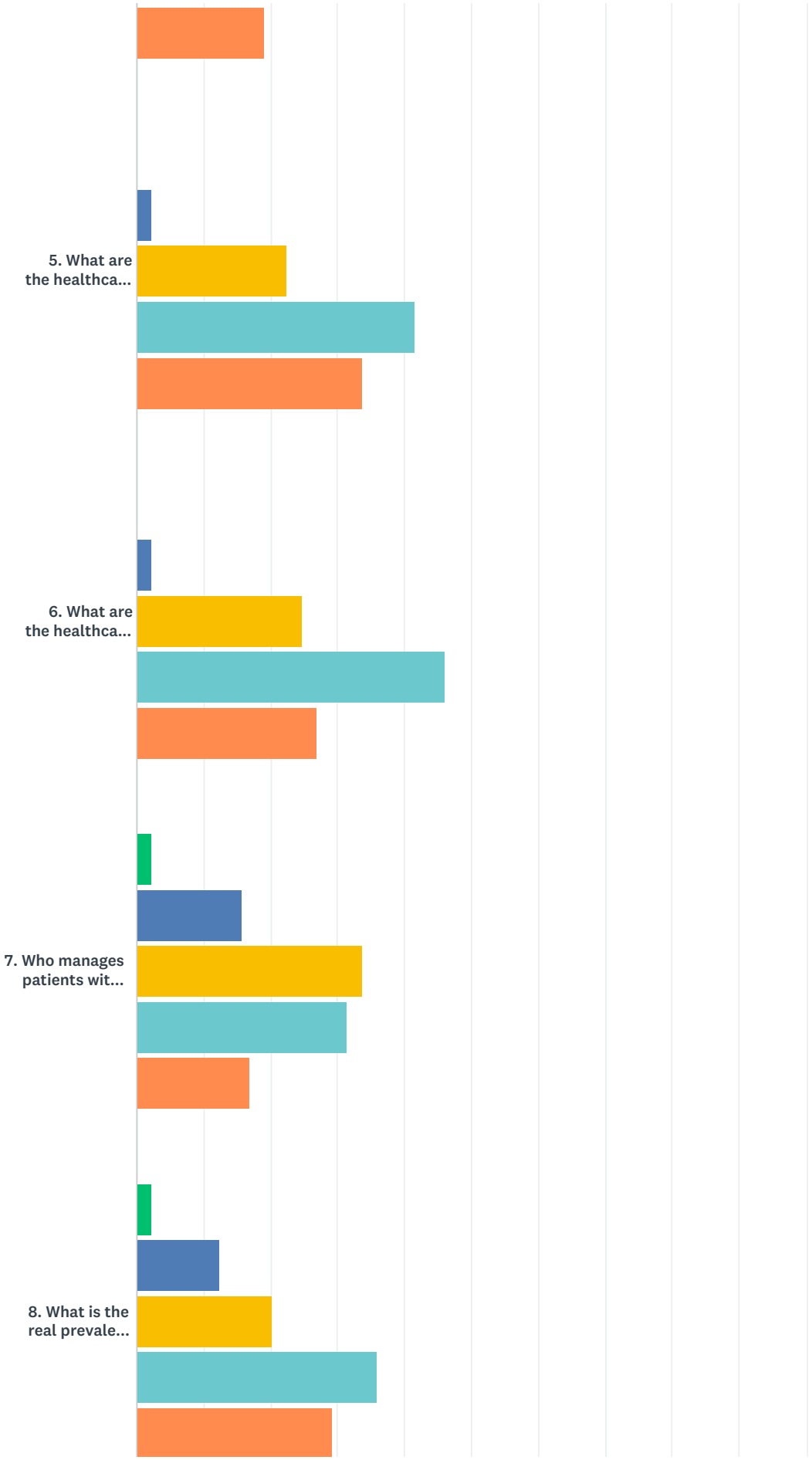


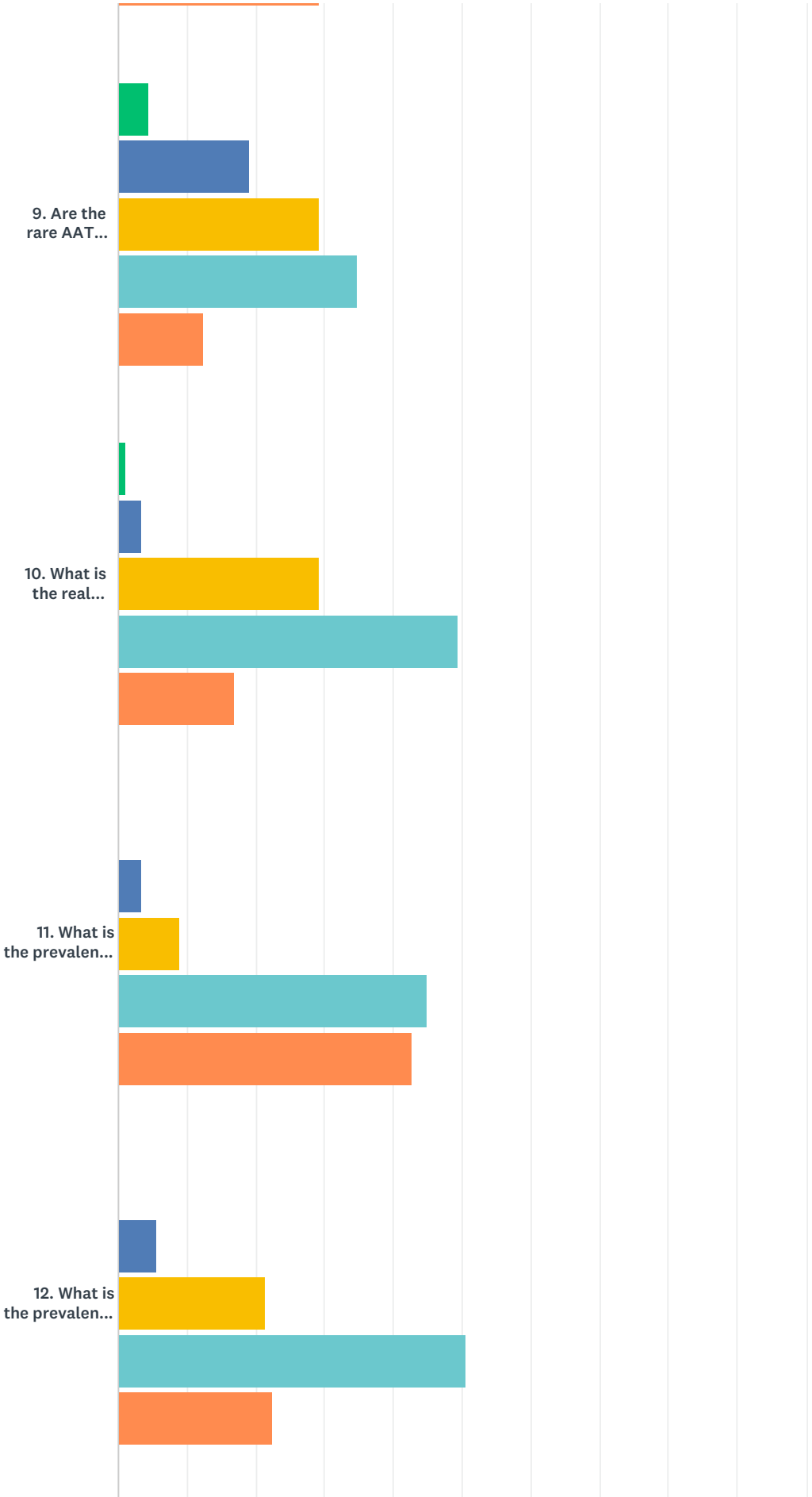
	YES	NO	UNKNOWN	TOTAL	WEIGHTED AVERAGE
licensed	77.66% 73	18.09% 17	4.26% 4	94	1.27
reimbursed on a regular basis	55.32% 52	42.55% 40	2.13% 2	94	1.47

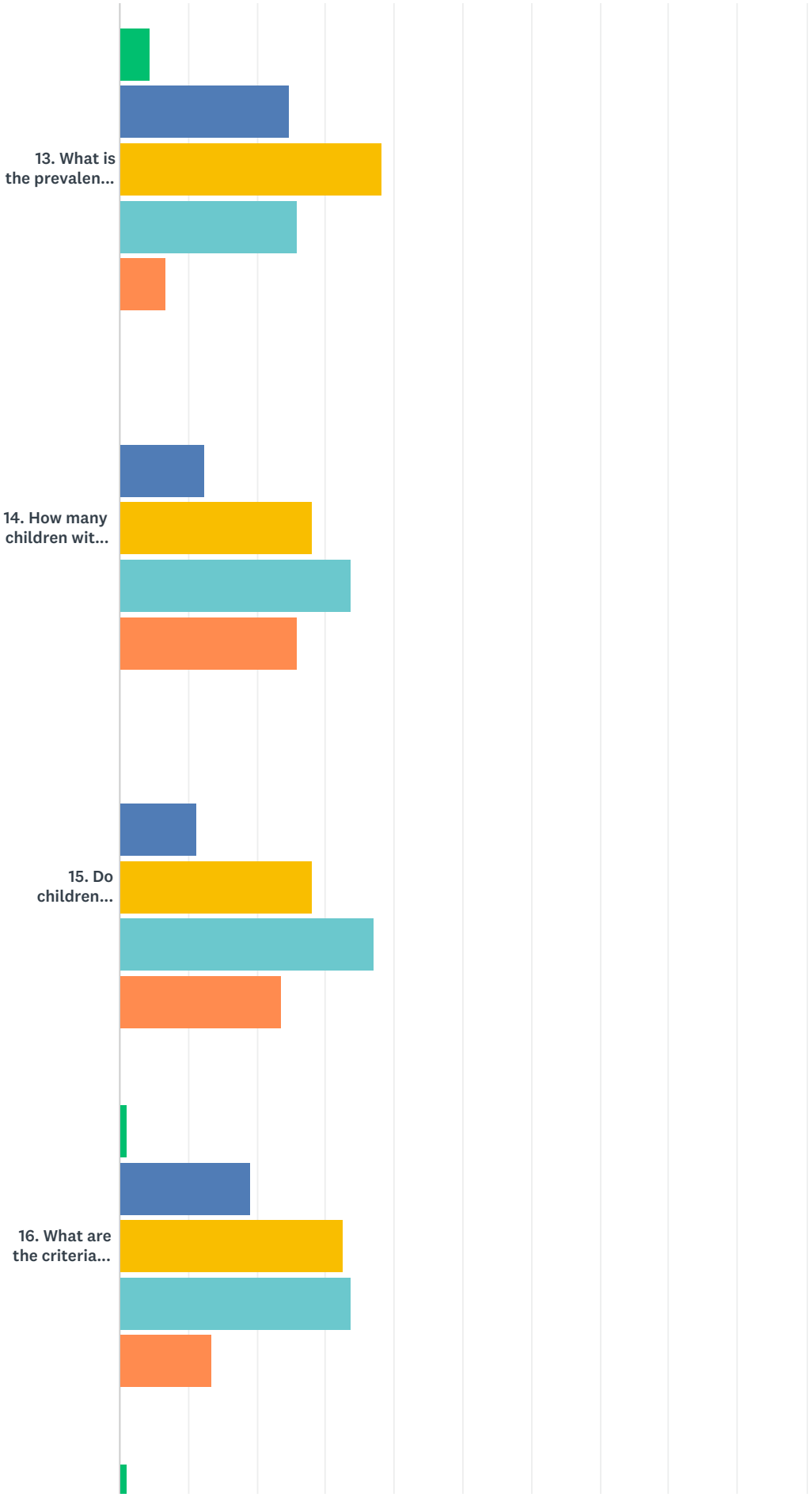
Q8 1. Epidemiology and natural course of the disease

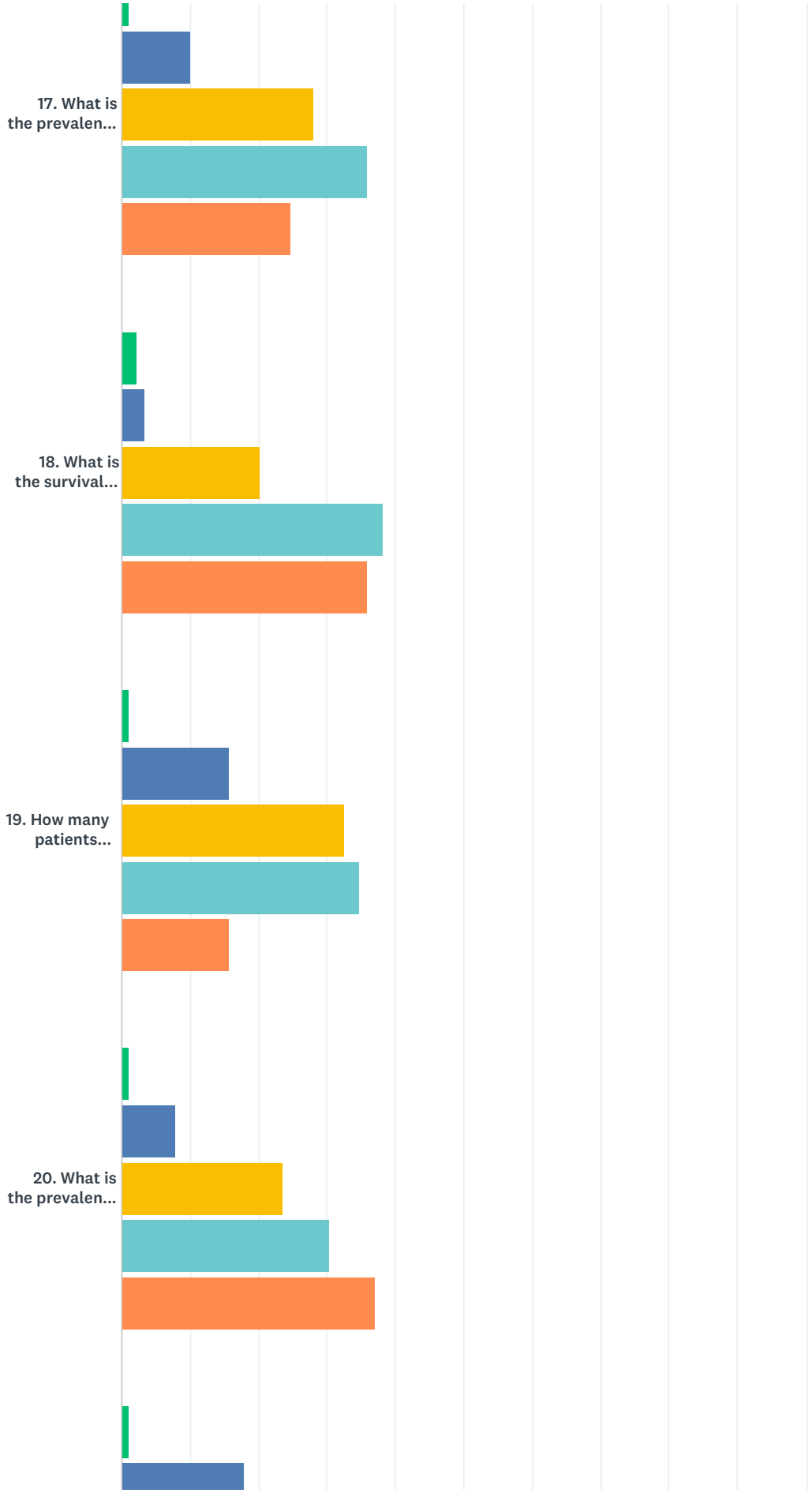
Answered: 89 Skipped: 5

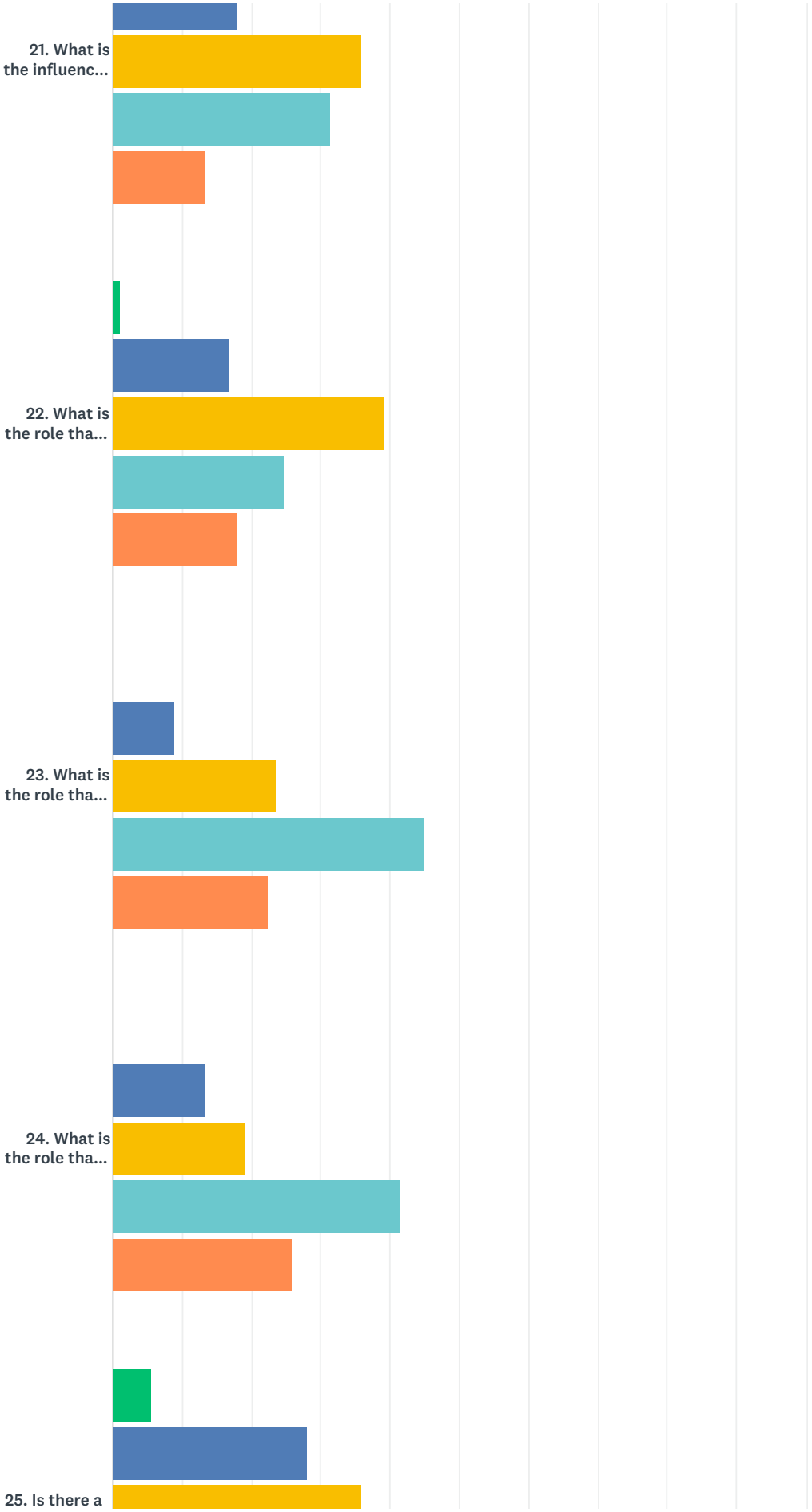


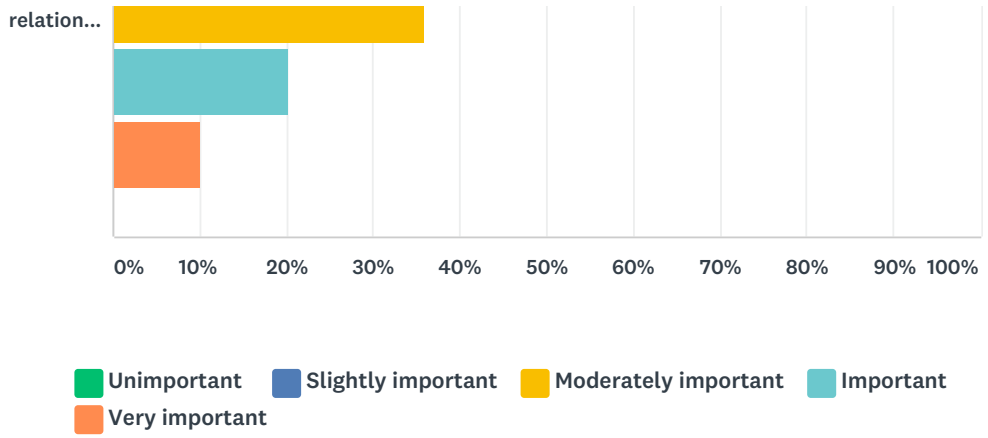

5. What are the healthca...
6. What are the healthca...
7. Who manages patients wit...
8. What is the real prevale...


9. Are the rare AAT...
10. What is the real...
11. What is the prevalen...
12. What is the prevalen...


13. What is the prevalen...
14. How many children wit...
15. Do children...
16. What are the criteria...


17. What is the prevalen...
18. What is the survival...
19. How many patients...
20. What is the prevalen...


21. What is the influenc...
22. What is the role tha...
23. What is the role tha...
24. What is the role tha...
25. Is there a



	UNIMPORTANT	SLIGHTLY IMPORTANT	MODERATELY IMPORTANT	IMPORTANT	VERY IMPORTANT	TOTAL	WEIGHTED AVERAGE
1. What is the prevalence of liver disease in AATD for the different protein phenotypes/genotypes?	0.00% 0	10.11% 9	32.58% 29	33.71% 30	23.60% 21	89	3.71
2. What is the prevalence of lung disease in never smoker MZ individuals?	4.49% 4	14.61% 13	16.85% 15	26.97% 24	37.08% 33	89	3.78
3. What is the prevalence of lung disease in smoker or ex smoker MZ individuals?	0.00% 0	4.49% 4	19.10% 17	34.83% 31	41.57% 37	89	4.13
4. What are the general healthcare costs related to AATD?	0.00% 0	7.87% 7	29.21% 26	43.82% 39	19.10% 17	89	3.74
5. What are the healthcare costs related to augmentation therapy in AATD?	0.00% 0	2.25% 2	22.47% 20	41.57% 37	33.71% 30	89	4.07
6. What are the healthcare costs related to lung disease in AATD?	0.00% 0	2.25% 2	24.72% 22	46.07% 41	26.97% 24	89	3.98
7. Who manages patients with AATD across Europe, including pulmonologists, gastroenterologists, internal medicine specialists, pediatricians or general practitioners?	2.25% 2	15.73% 14	33.71% 30	31.46% 28	16.85% 15	89	3.45
8. What is the real prevalence of rare AAT deficient variants?	2.25% 2	12.36% 11	20.22% 18	35.96% 32	29.21% 26	89	3.78
9. Are the rare AAT deficient variants more frequent in those countries in which the gene frequency of PiZZ is lower?	4.49% 4	19.10% 17	29.21% 26	34.83% 31	12.36% 11	89	3.31

10. What is the real frequency and type of bronchiectasis in AATD?	1.12% 1	3.37% 3	29.21% 26	49.44% 44	16.85% 15	89	3.78
11. What is the prevalence of emphysema among never smokers PiZZ?	0.00% 0	3.37% 3	8.99% 8	44.94% 40	42.70% 38	89	4.27
12. What is the prevalence of coexistent lung and liver disease among AATD individuals?	0.00% 0	5.62% 5	21.35% 19	50.56% 45	22.47% 20	89	3.90
13. What is the prevalence of other less frequent manifestations, such as panniculitis?	4.49% 4	24.72% 22	38.20% 34	25.84% 23	6.74% 6	89	3.06
14. How many children with liver diseases have lung and or liver problems later in life?	0.00% 0	12.36% 11	28.09% 25	33.71% 30	25.84% 23	89	3.73
15. Do children without signs of liver problems develop lung/liver problems just as often later?	0.00% 0	11.24% 10	28.09% 25	37.08% 33	23.60% 21	89	3.73
16. What are the criteria to consider the rare/ultra-rare SERPINA1 aberration as clinically important?	1.12% 1	19.10% 17	32.58% 29	33.71% 30	13.48% 12	89	3.39
17. What is the prevalence of patients referred to lung or liver transplant; how many of them actually receive a transplant?	1.12% 1	10.11% 9	28.09% 25	35.96% 32	24.72% 22	89	3.73
18. What is the survival of AATD patients receiving a lung transplant?	2.25% 2	3.37% 3	20.22% 18	38.20% 34	35.96% 32	89	4.02
19. How many patients receive surgical or endoscopic lung volume reduction (LVR)?	1.12% 1	15.73% 14	32.58% 29	34.83% 31	15.73% 14	89	3.48
20. What is the prevalence of never smokers PiZZ without lung disease?	1.12% 1	7.87% 7	23.60% 21	30.34% 27	37.08% 33	89	3.94
21. What is the influence of race, sex and socioeconomic status on the natural history and pathobiology of AATD?	1.12% 1	17.98% 16	35.96% 32	31.46% 28	13.48% 12	89	3.38

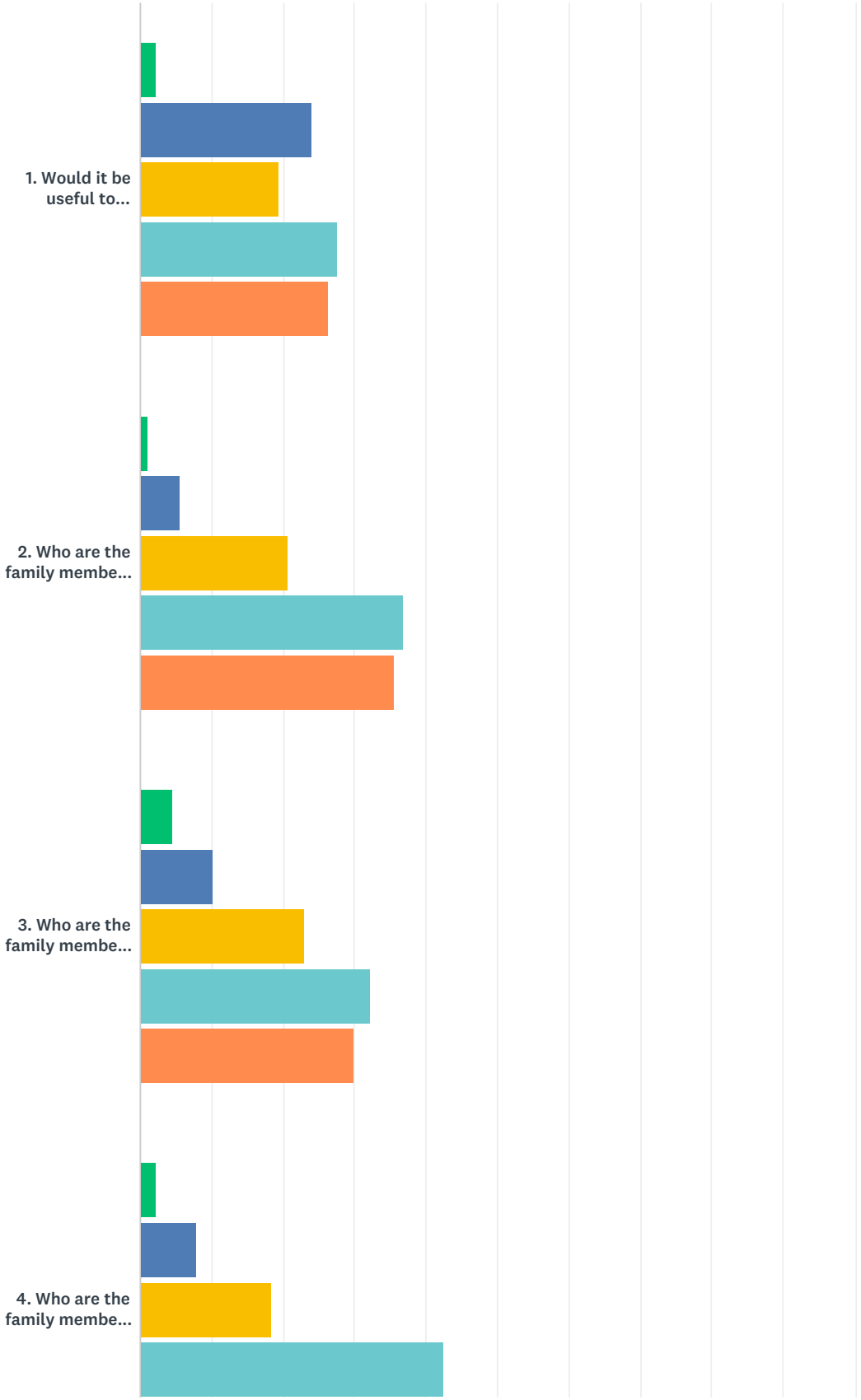
22. What is the role that the electronic cigarette might have in the development of lung disease in AATD?	1.12% 1	16.85% 15	39.33% 35	24.72% 22	17.98% 16	89	3.42
23. What is the role that pollution might have in the development of lung disease in AATD?	0.00% 0	8.99% 8	23.60% 21	44.94% 40	22.47% 20	89	3.81
24. What is the role that work exposures might have in the development of lung disease in AATD?	0.00% 0	13.48% 12	19.10% 17	41.57% 37	25.84% 23	89	3.80
25. Is there a relation between AATD and cystic fibrosis?	5.62% 5	28.09% 25	35.96% 32	20.22% 18	10.11% 9	89	3.01

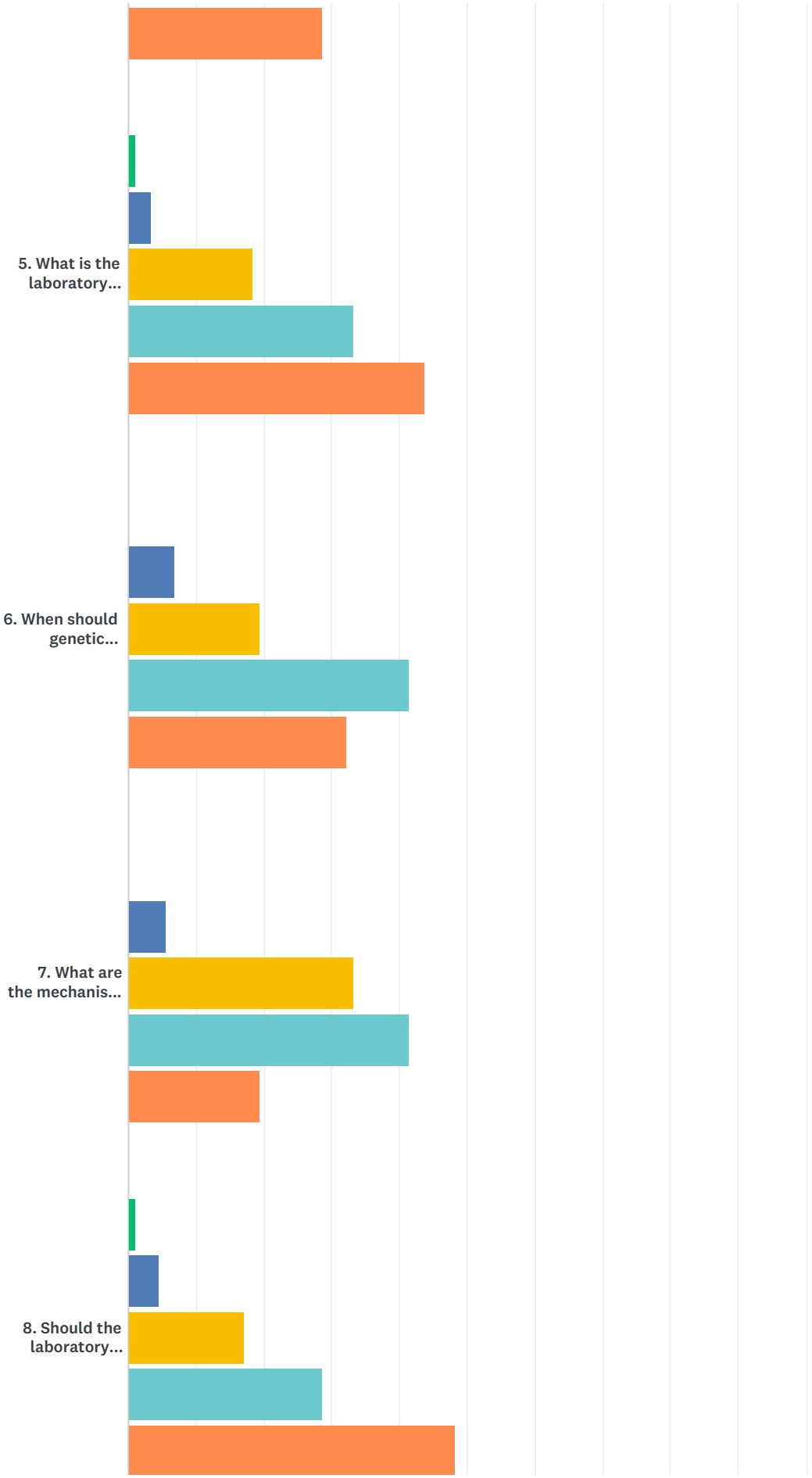
Q9 Please indicate if you have any additional research priorities that you considered necessary to include or have any further comments for the ‘Epidemiology and natural course of the disease‘ research area:

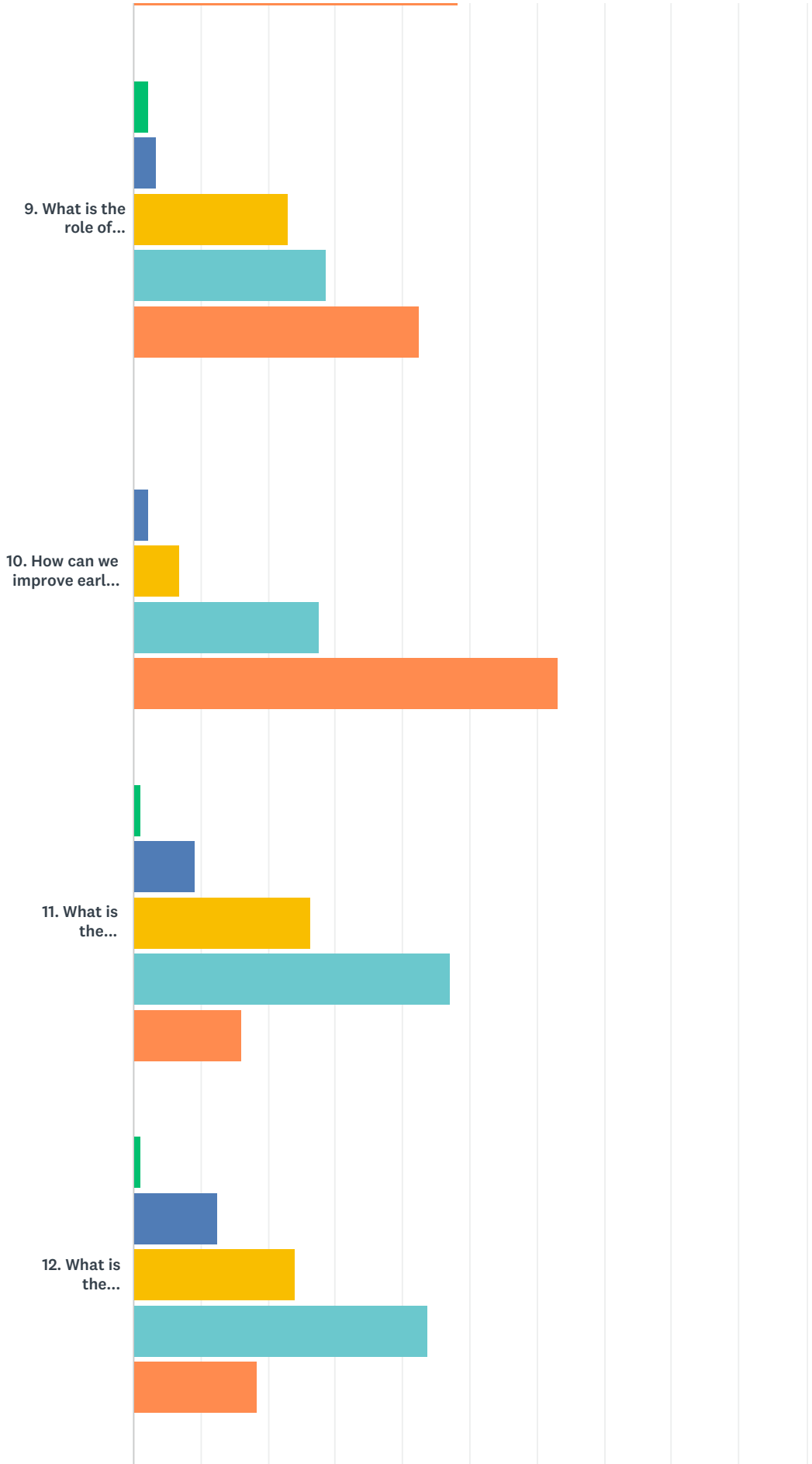
Answered: 12 Skipped: 82

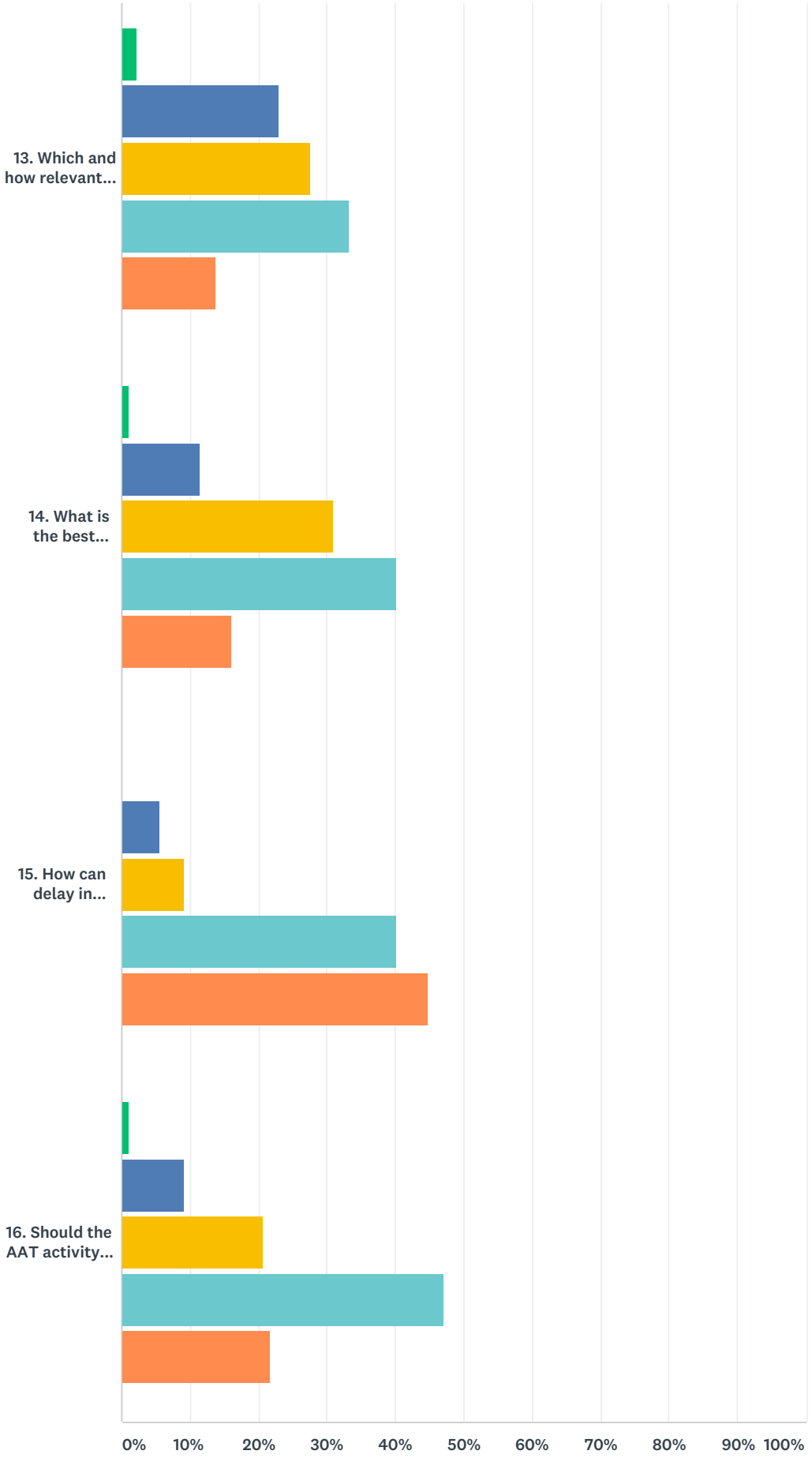
Q10 2. Diagnostic and screening

Answered: 87 Skipped: 7




5. What is the laboratory...
6. When should genetic...
7. What are the mechanis...
8. Should the laboratory...


9. What is the role of...
10. How can we improve earl...
11. What is the...
12. What is the...


13. Which and how relevant...
14. What is the best...
15. How can delay in...
16. Should the AAT activity...
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%

	UNIMPORTANT	SLIGHTLY IMPORTANT	MODERATELY IMPORTANT	IMPORTANT	VERY IMPORTANT	TOTAL	WEIGHTED AVERAGE
1. Would it be useful to include AAT in the current newborn screening program?	2.30% 2	24.14% 21	19.54% 17	27.59% 24	26.44% 23	87	3.52
2. Who are the family members of a patient PI*ZZ that should be screened for AATD?	1.15% 1	5.75% 5	20.69% 18	36.78% 32	35.63% 31	87	4.00
3. Who are the family members of a patient PI*MZ that should be screened for AATD?	4.60% 4	10.34% 9	22.99% 20	32.18% 28	29.89% 26	87	3.72
4. Who are the family members of a patient PI*SZ that should be screened for AATD?	2.30% 2	8.05% 7	18.39% 16	42.53% 37	28.74% 25	87	3.87
5. What is the laboratory algorithm that should be used for family screening?	1.15% 1	3.45% 3	18.39% 16	33.33% 29	43.68% 38	87	4.15
6. When should genetic counseling be offered to AATD patients?	0.00% 0	6.90% 6	19.54% 17	41.38% 36	32.18% 28	87	3.99
7. What are the mechanisms involved in the initiation, maintenance, and hereditability of the epigenetic changes observed in AATD?	0.00% 0	5.75% 5	33.33% 29	41.38% 36	19.54% 17	87	3.75
8. Should the laboratory diagnosis algorithm be standardized in Europe?	1.15% 1	4.60% 4	17.24% 15	28.74% 25	48.28% 42	87	4.18
9. What is the role of European certified laboratories for AATD diagnosis?	2.30% 2	3.45% 3	22.99% 20	28.74% 25	42.53% 37	87	4.06
10. How can we improve early and accurate diagnosis in AATD?	0.00% 0	2.30% 2	6.90% 6	27.59% 24	63.22% 55	87	4.52
11. What is the psychological effect that the diagnosis might have in asymptomatic individuals?	1.15% 1	9.20% 8	26.44% 23	47.13% 41	16.09% 14	87	3.68

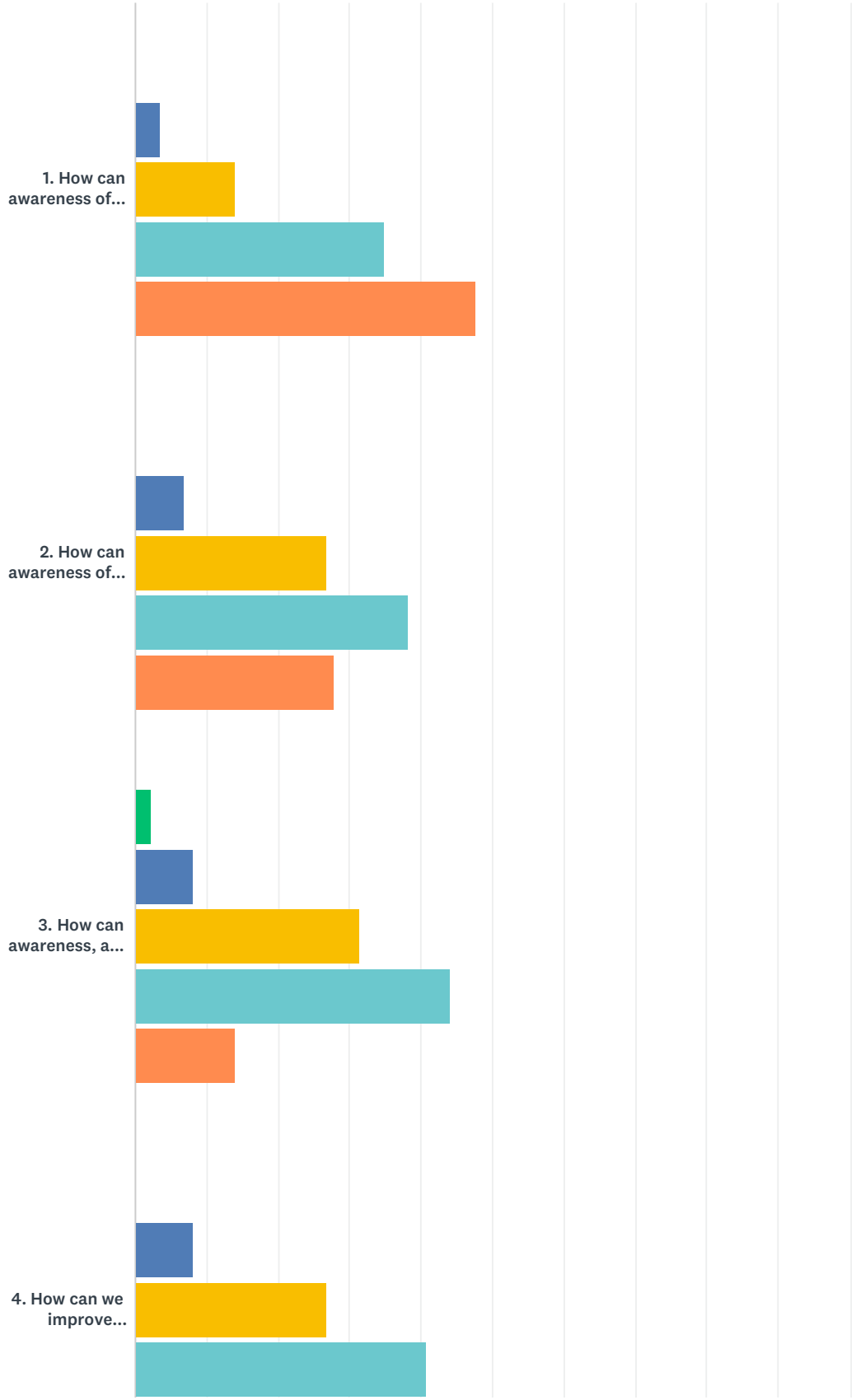
12. What is the psychological burden of childhood diagnosis for parents and during the individuals development?	1.15% 1	12.64% 11	24.14% 21	43.68% 38	18.39% 16	87	3.66
13. Which and how relevant are the economic implications after diagnosis for asymptomatic individuals? (health insurance, work environment…)	2.30% 2	22.99% 20	27.59% 24	33.33% 29	13.79% 12	87	3.33
14. What is the best approach to genetic testing considering the potential negative impacts for AATD patients?	1.15% 1	11.49% 10	31.03% 27	40.23% 35	16.09% 14	87	3.59
15. How can delay in diagnosis be reduced?	0.00% 0	5.75% 5	9.20% 8	40.23% 35	44.83% 39	87	4.24
16. Should the AAT activity testing be a part of standard diagnostic algorithm for rare SERPINA 1 mutations?	1.15% 1	9.20% 8	20.69% 18	47.13% 41	21.84% 19	87	3.79

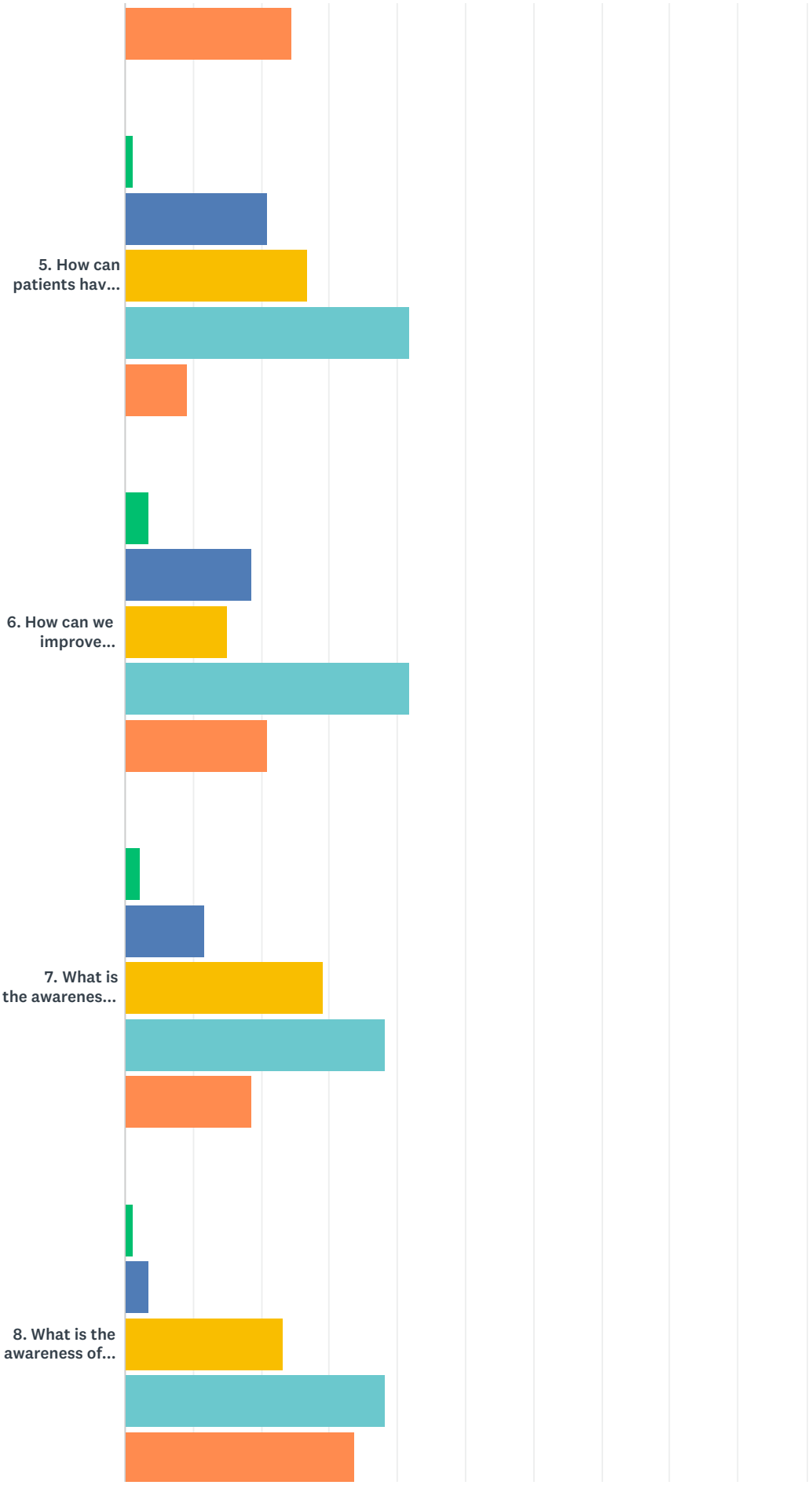
Q11 Please indicate if you have any additional research priorities that you considered necessary to include or have any further comments for the ‘Diagnostic and screening‘ research area:

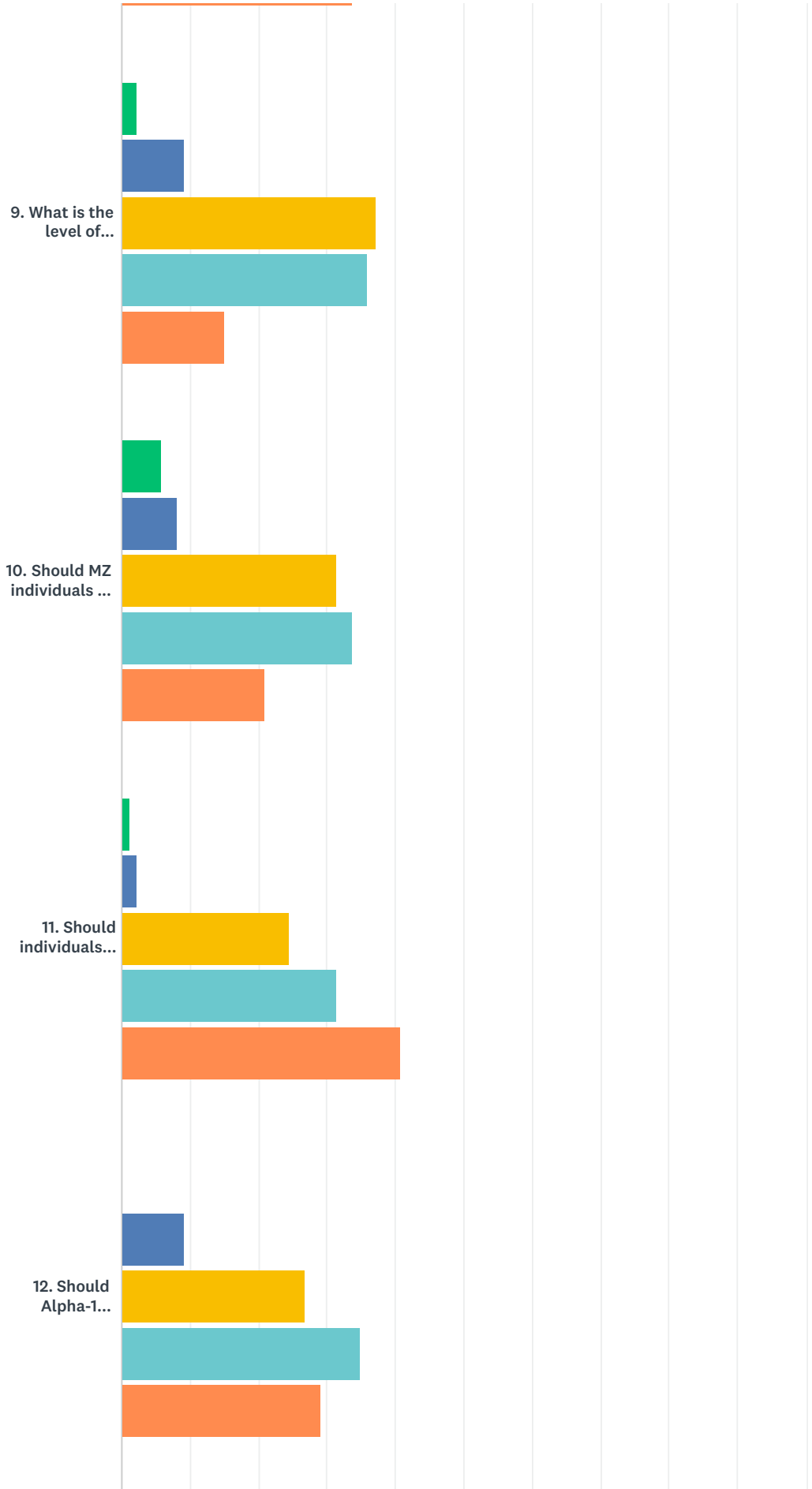
Answered: 7 Skipped: 87

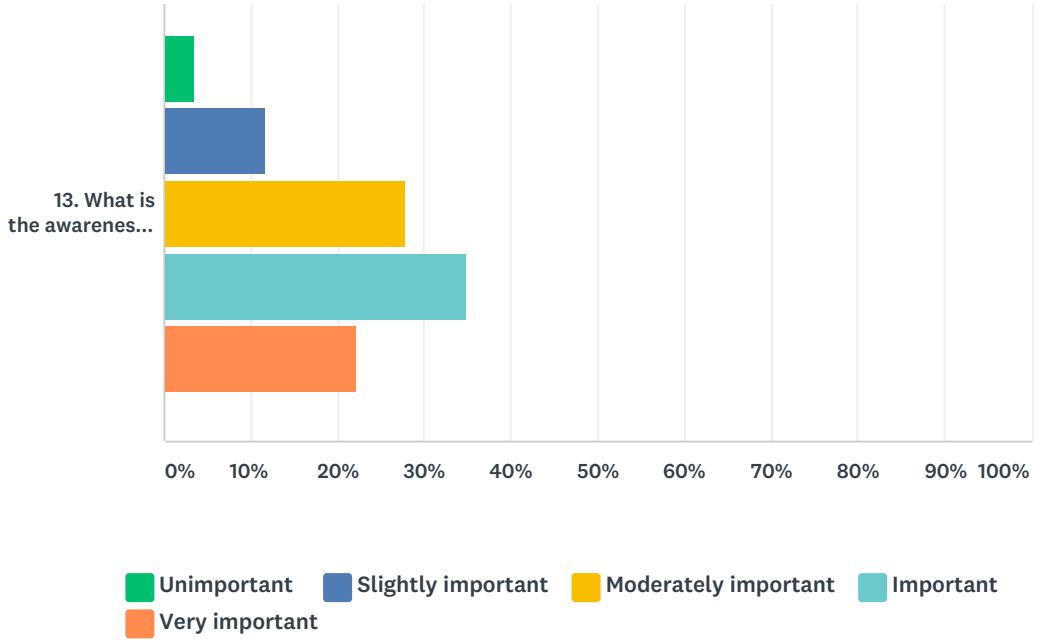
Q12 3. Awareness and education for HCP and for patients. Registries

Answered: 86 Skipped: 8




5. How can patients hav...
6. How can we improve...
7. What is the awarenes...
8. What is the awareness of...


9. What is the level of...
10. Should MZ individuals ...
11. Should individuals...
12. Should Alpha-1...



	UNIMPORTANT	SLIGHTLY IMPORTANT	MODERATELY IMPORTANT	IMPORTANT	VERY IMPORTANT	TOTAL	WEIGHTED AVERAGE
1. How can awareness of AATD, among physicians, be improved?	0.00% 0	3.49% 3	13.95% 12	34.88% 30	47.67% 41	86	4.27
2. How can awareness of AATD in community care services be improved?	0.00% 0	6.98% 6	26.74% 23	38.37% 33	27.91% 24	86	3.87
3. How can awareness, and use of peer support forums and social media to exchange information about AATD, be raised?	2.33% 2	8.14% 7	31.40% 27	44.19% 38	13.95% 12	86	3.59
4. How can we improve communication/quality information from HCP to AATD patients?	0.00% 0	8.14% 7	26.74% 23	40.70% 35	24.42% 21	86	3.81
5. How can patients have and use equipment at home to monitor their symptoms?	1.16% 1	20.93% 18	26.74% 23	41.86% 36	9.30% 8	86	3.37
6. How can we improve transition from pediatrics to adult care in AATD patients diagnosed during childhood?	3.49% 3	18.60% 16	15.12% 13	41.86% 36	20.93% 18	86	3.58
7. What is the awareness of pediatricians regarding AATD manifestations in adult life and how can we improve it?	2.33% 2	11.63% 10	29.07% 25	38.37% 33	18.60% 16	86	3.59

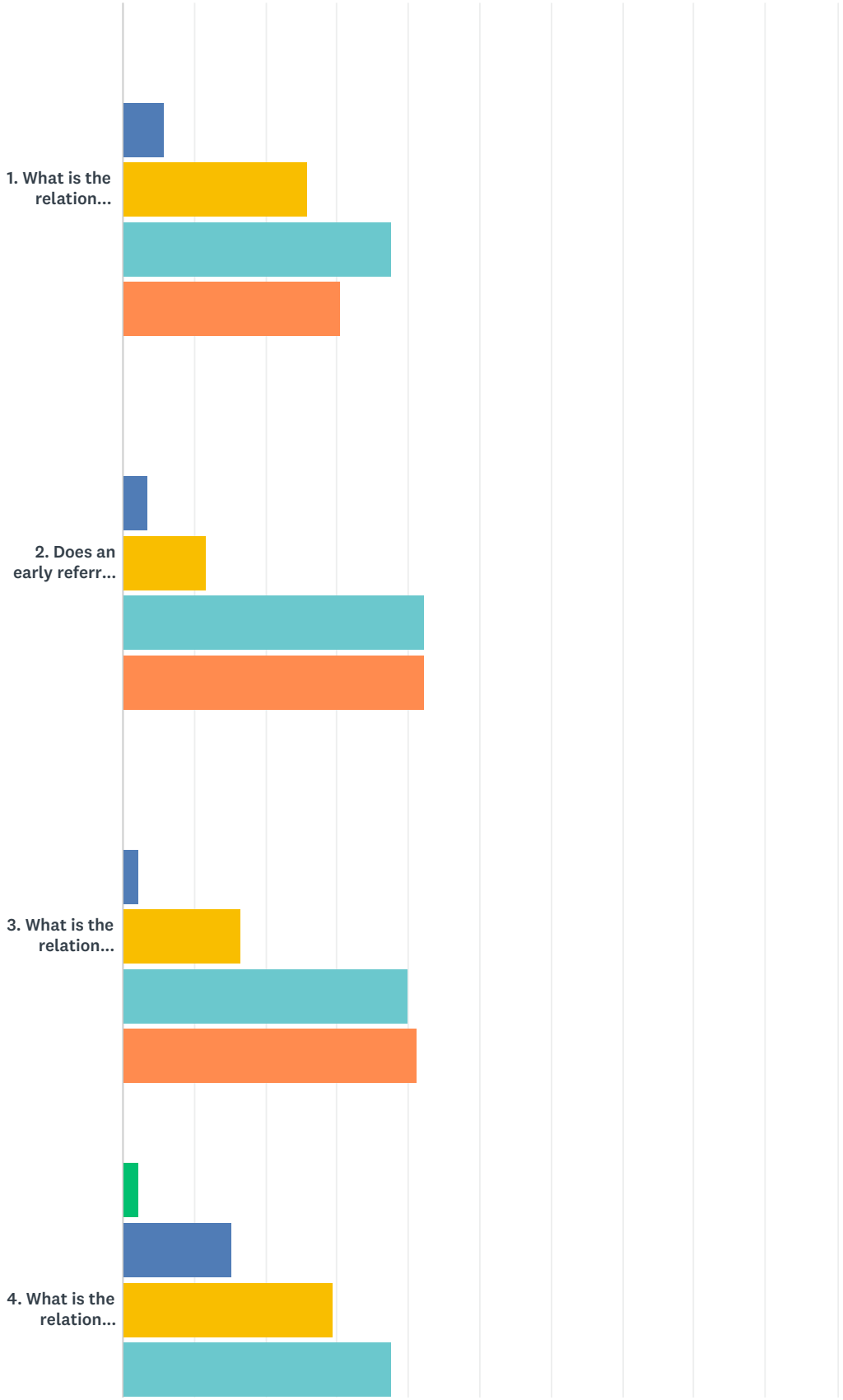
8. What is the awareness of respiratory specialists regarding non-COPD AATD manifestations (including respiratory) in adults and how can we improve it?	1.16% 1	3.49% 3	23.26% 20	38.37% 33	33.72% 29	86	4.00
9. What is the level of satisfaction that AATD patients have regarding management and research of AATD within the medical community?	2.33% 2	9.30% 8	37.21% 32	36.05% 31	15.12% 13	86	3.52
10. Should MZ individuals be included in AATD registries?	5.81% 5	8.14% 7	31.40% 27	33.72% 29	20.93% 18	86	3.56
11. Should individuals with rare mutations be included in AATD registries?	1.16% 1	2.33% 2	24.42% 21	31.40% 27	40.70% 35	86	4.08
12. Should Alpha-1 guidelines be established for all countries that prescribe testing of Alpha-1 in case of COPD, asthma and other indications, or is the European guideline sufficient?	0.00% 0	9.30% 8	26.74% 23	34.88% 30	29.07% 25	86	3.84
13. What is the awareness of pediatricians regarding AATD manifestations in childhood?	3.49% 3	11.63% 10	27.91% 24	34.88% 30	22.09% 19	86	3.60

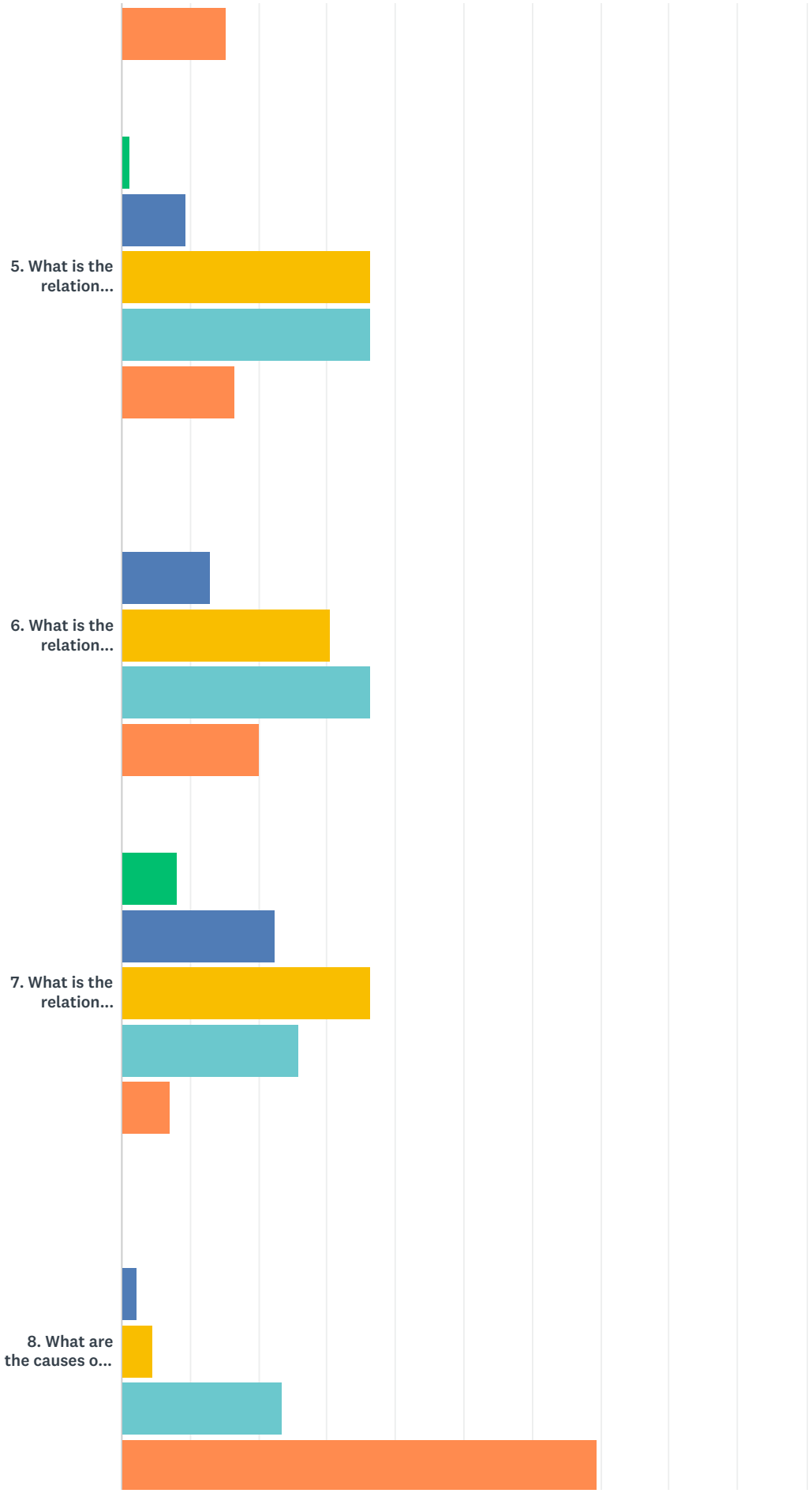
Q13 Please indicate if you have any additional research priorities that you considered necessary to include or have any further comments for the ‘Awareness and education for HCP and for patients. Registries‘ research area:

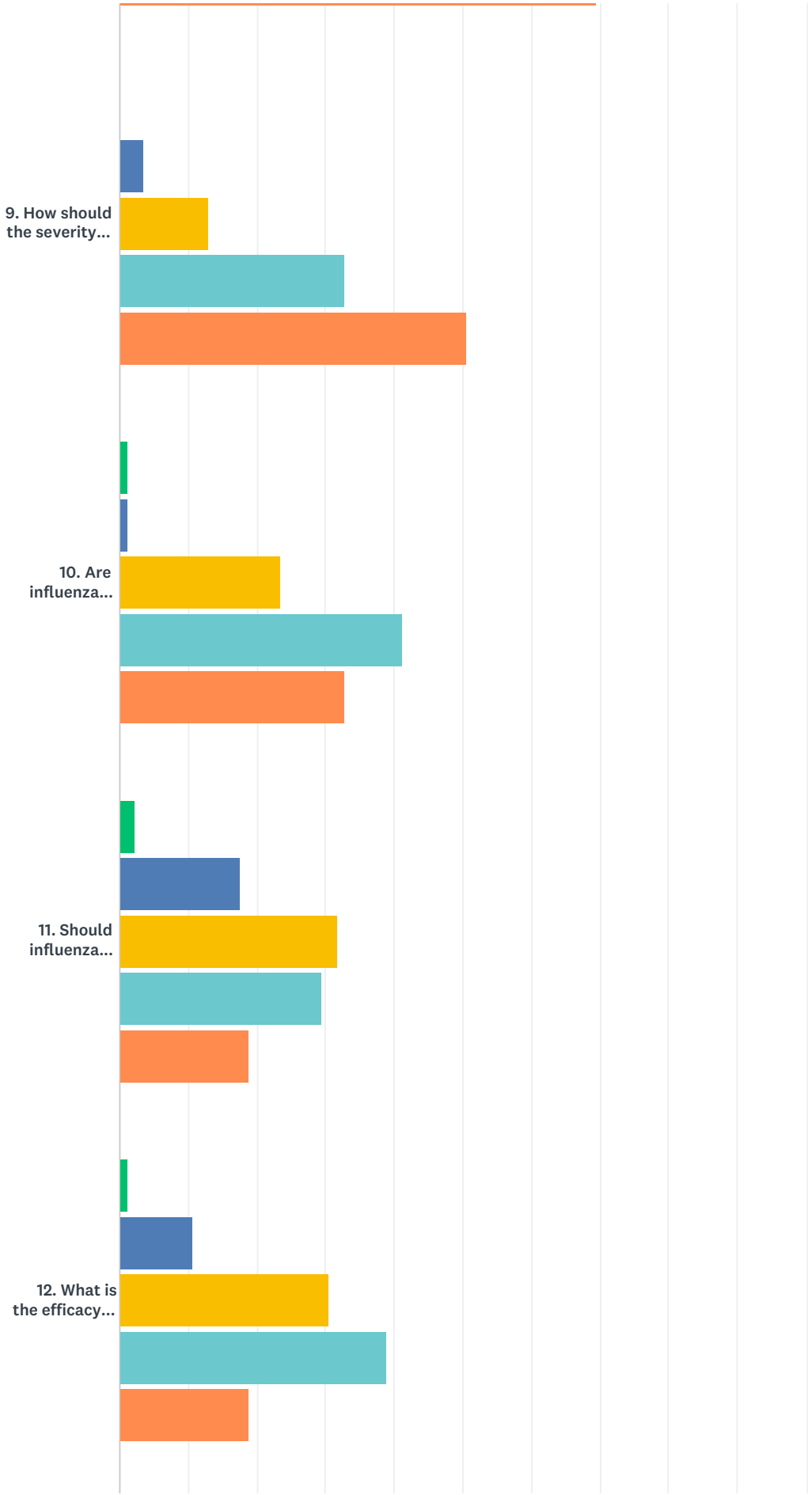
Answered: 6 Skipped: 88

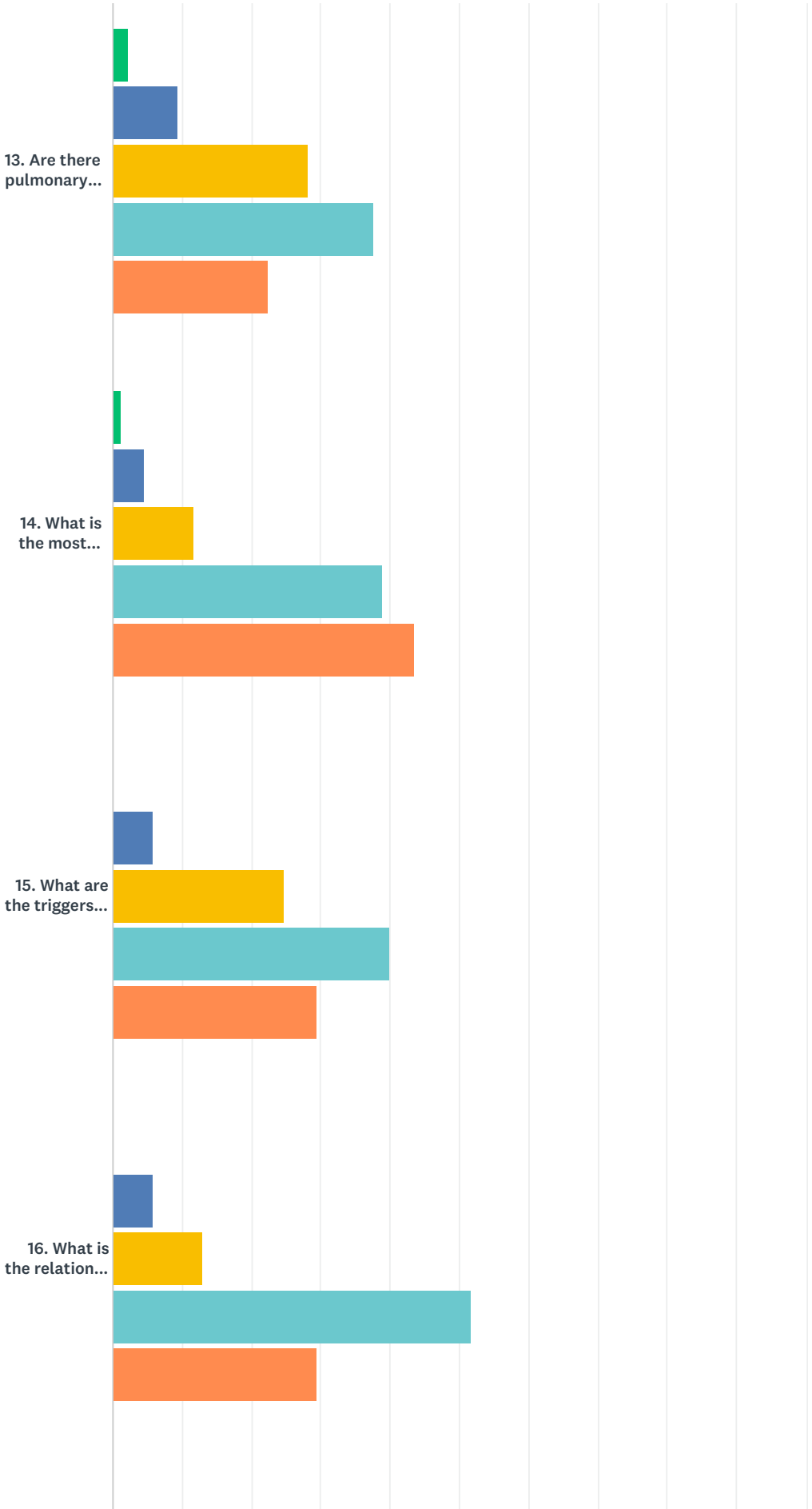
Q14 4. Clinical manifestations

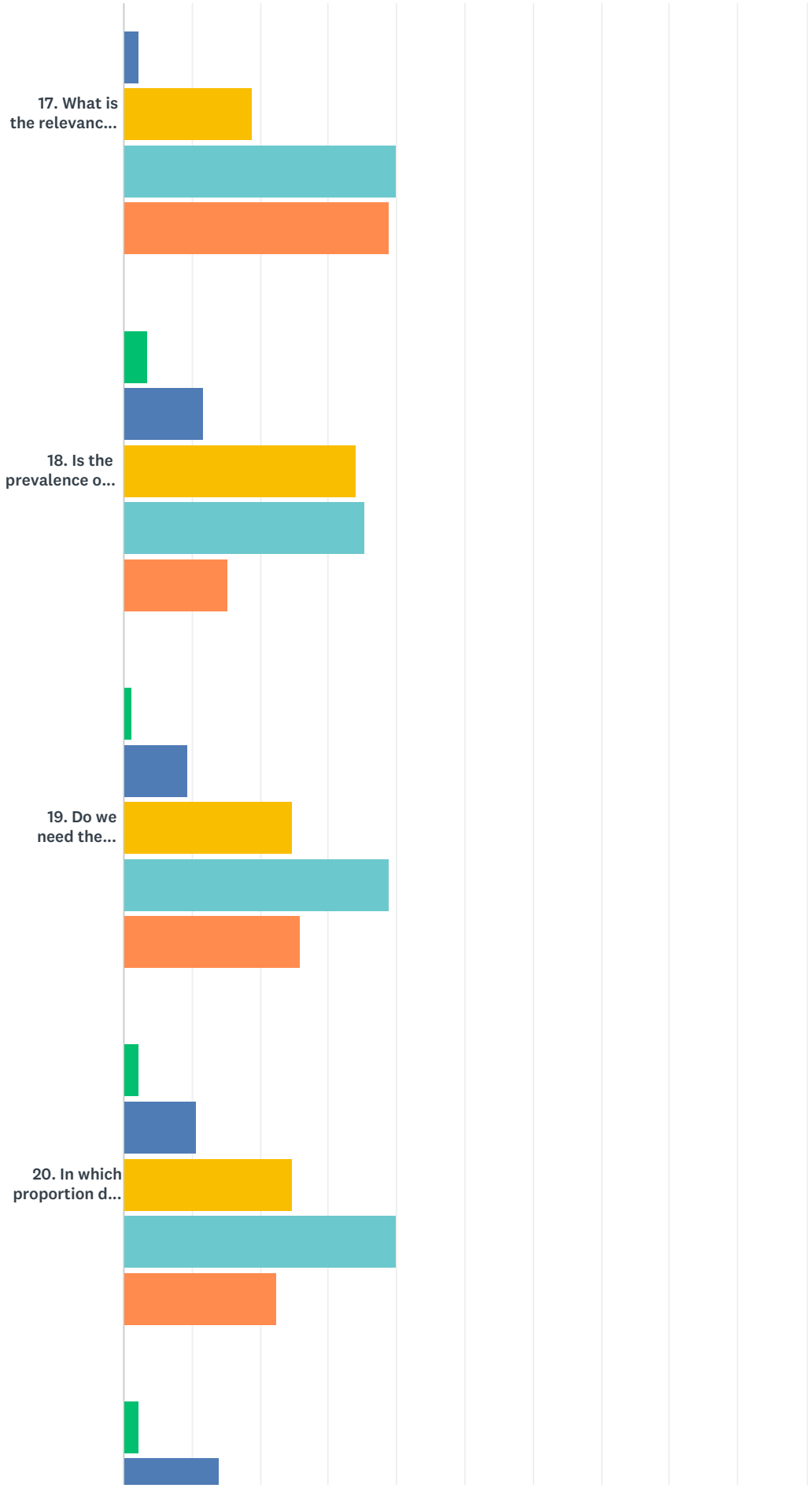
Answered: 85 Skipped: 9

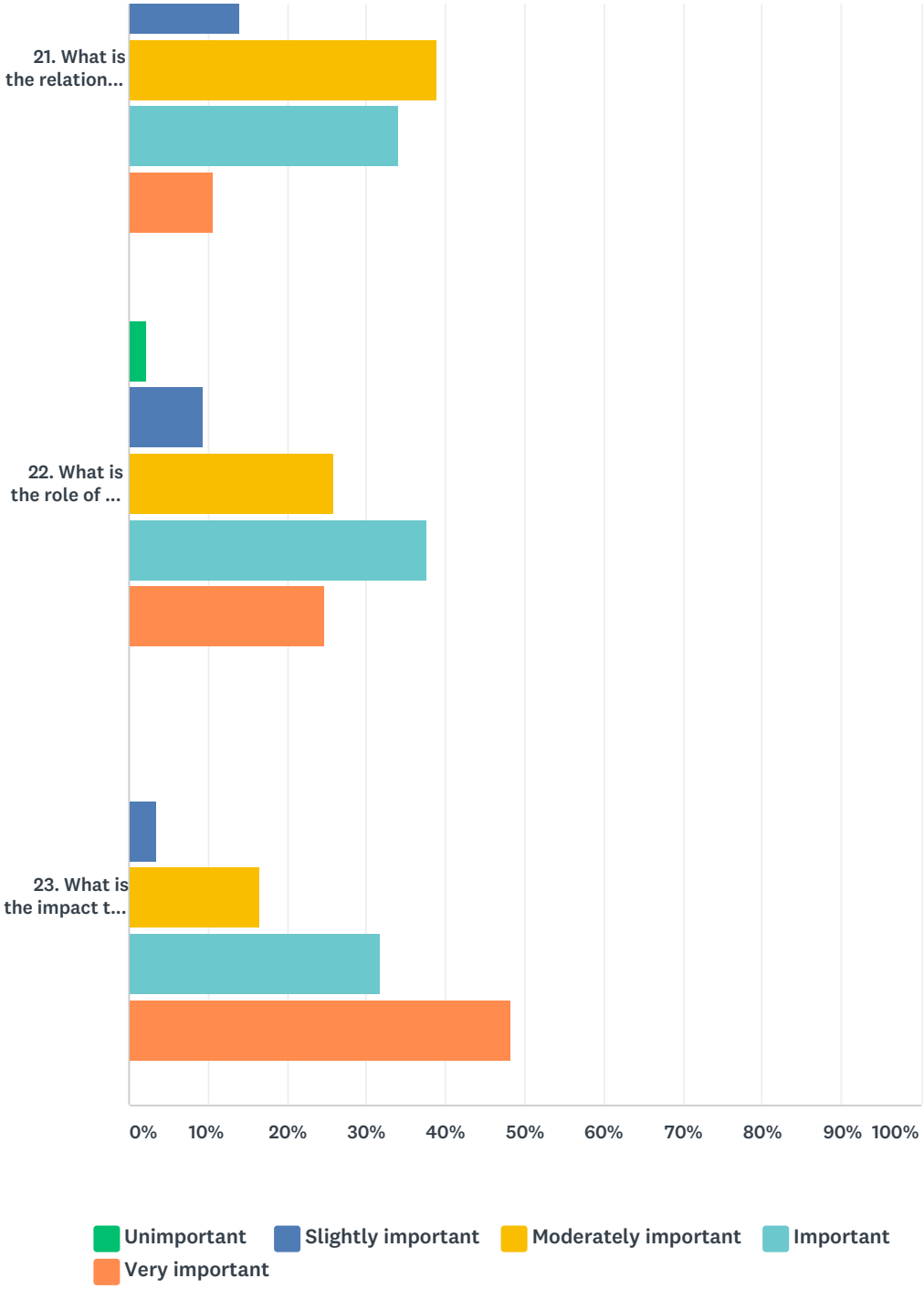



5. What is the relation...
6. What is the relation...
7. What is the relation...
8. What are the causes o...


9. How should the severity...
10. Are influenza...
11. Should influenza...
12. What is the efficacy...


13. Are there pulmonary...
14. What is the most...
15. What are the triggers...
16. What is the relation...


17. What is the relevanc...
18. Is the prevalence o...
19. Do we need the...
20. In which proportion d...



	UNIMPORTANT	SLIGHTLY IMPORTANT	MODERATELY IMPORTANT	IMPORTANT	VERY IMPORTANT	TOTAL	WEIGHTED AVERAGE
1. What is the relation between asthma and AATD?	0.00% 0	5.88% 5	25.88% 22	37.65% 32	30.59% 26	85	3.93
2. Does an early referral to a specialist in AATD change outcome in patients?	0.00% 0	3.53% 3	11.76% 10	42.35% 36	42.35% 36	85	4.24
3. What is the relation between bronchiectasis and AATD?	0.00% 0	2.35% 2	16.47% 14	40.00% 34	41.18% 35	85	4.20

4. What is the relation between aneurisms and AATD?	2.35% 2	15.29% 13	29.41% 25	37.65% 32	15.29% 13	85	3.48
5. What is the relation between AATD and cardiac comorbidities such as cardiac disfunction and aortic dissection?	1.18% 1	9.41% 8	36.47% 31	36.47% 31	16.47% 14	85	3.58
6. What is the relation between cancer and AATD?	0.00% 0	12.94% 11	30.59% 26	36.47% 31	20.00% 17	85	3.64
7. What is the relation between fibromyalgia and AATD?	8.24% 7	22.35% 19	36.47% 31	25.88% 22	7.06% 6	85	3.01
8. What are the causes of fast progression and poor outcome in patients with AATD?	0.00% 0	2.35% 2	4.71% 4	23.53% 20	69.41% 59	85	4.60
9. How should the severity of an exacerbation, in AATD patients, be assessed and what is its impact on long-term outcomes?	0.00% 0	3.53% 3	12.94% 11	32.94% 28	50.59% 43	85	4.31
10. Are influenza and/or pneumococcal vaccines effective in preventing exacerbations in patients with AATD?	1.18% 1	1.18% 1	23.53% 20	41.18% 35	32.94% 28	85	4.04
11. Should influenza and/or pneumococcal vaccines be prescribed to asymptomatic heterozygote patients?	2.35% 2	17.65% 15	31.76% 27	29.41% 25	18.82% 16	85	3.45
12. What is the efficacy and advisability of vaccination against hepatitis B in AATD patients?	1.18% 1	10.59% 9	30.59% 26	38.82% 33	18.82% 16	85	3.64
13. Are there pulmonary manifestations in children with AATD?	2.35% 2	9.41% 8	28.24% 24	37.65% 32	22.35% 19	85	3.68
14. What is the most appropriate AAT blood concentration to consider severe and intermediate AATD?	1.18% 1	4.71% 4	11.76% 10	38.82% 33	43.53% 37	85	4.19
15. What are the triggers for an exacerbation in AATD patients?	0.00% 0	5.88% 5	24.71% 21	40.00% 34	29.41% 25	85	3.93
16. What is the relation between AATD and exacerbations?	0.00% 0	5.88% 5	12.94% 11	51.76% 44	29.41% 25	85	4.05

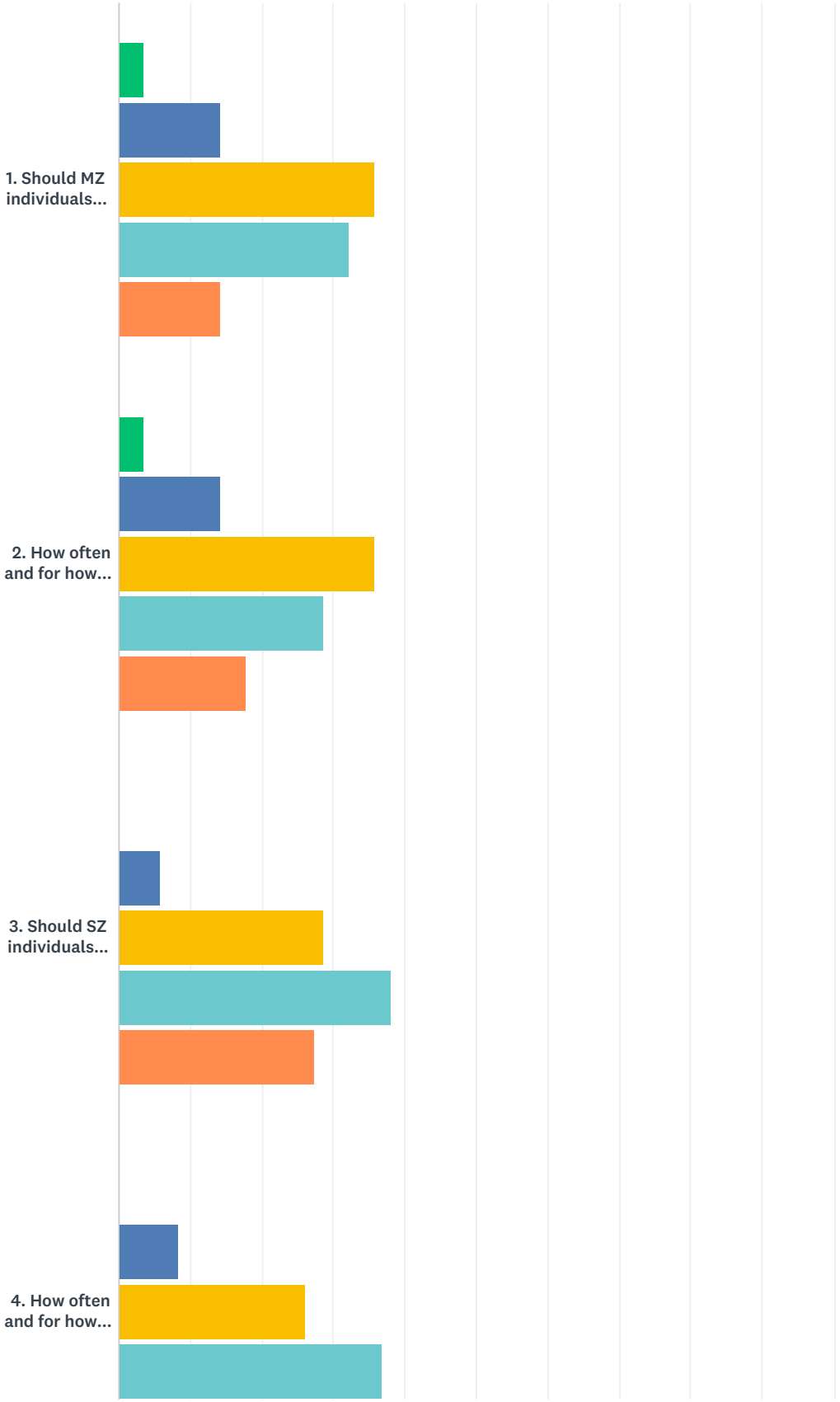
17. What is the relevance that impaired AAT activity might have in the development of lung disease?	0.00% 0	2.35% 2	18.82% 16	40.00% 34	38.82% 33	85	4.15
18. Is the prevalence of ACO in AATD the same as in COPD?	3.53% 3	11.76% 10	34.12% 29	35.29% 30	15.29% 13	85	3.47
19. Do we need the pan-European detailed clinical SOP for AATD patients follow-up? How different would it be for healthy AATDs (PiZZ) or PiMZ patients with COPD?	1.18% 1	9.41% 8	24.71% 21	38.82% 33	25.88% 22	85	3.79
20. In which proportion does AAT increase during inflammation?	2.35% 2	10.59% 9	24.71% 21	40.00% 34	22.35% 19	85	3.69
21. What is the relation between p-ANCA vasculitis and AATD?	2.35% 2	14.12% 12	38.82% 33	34.12% 29	10.59% 9	85	3.36
22. What is the role of the lung microbiome in the pathogenesis of AATD?	2.35% 2	9.41% 8	25.88% 22	37.65% 32	24.71% 21	85	3.73
23. What is the impact that the delay of diagnosis has in the prognosis of the disease?	0.00% 0	3.53% 3	16.47% 14	31.76% 27	48.24% 41	85	4.25

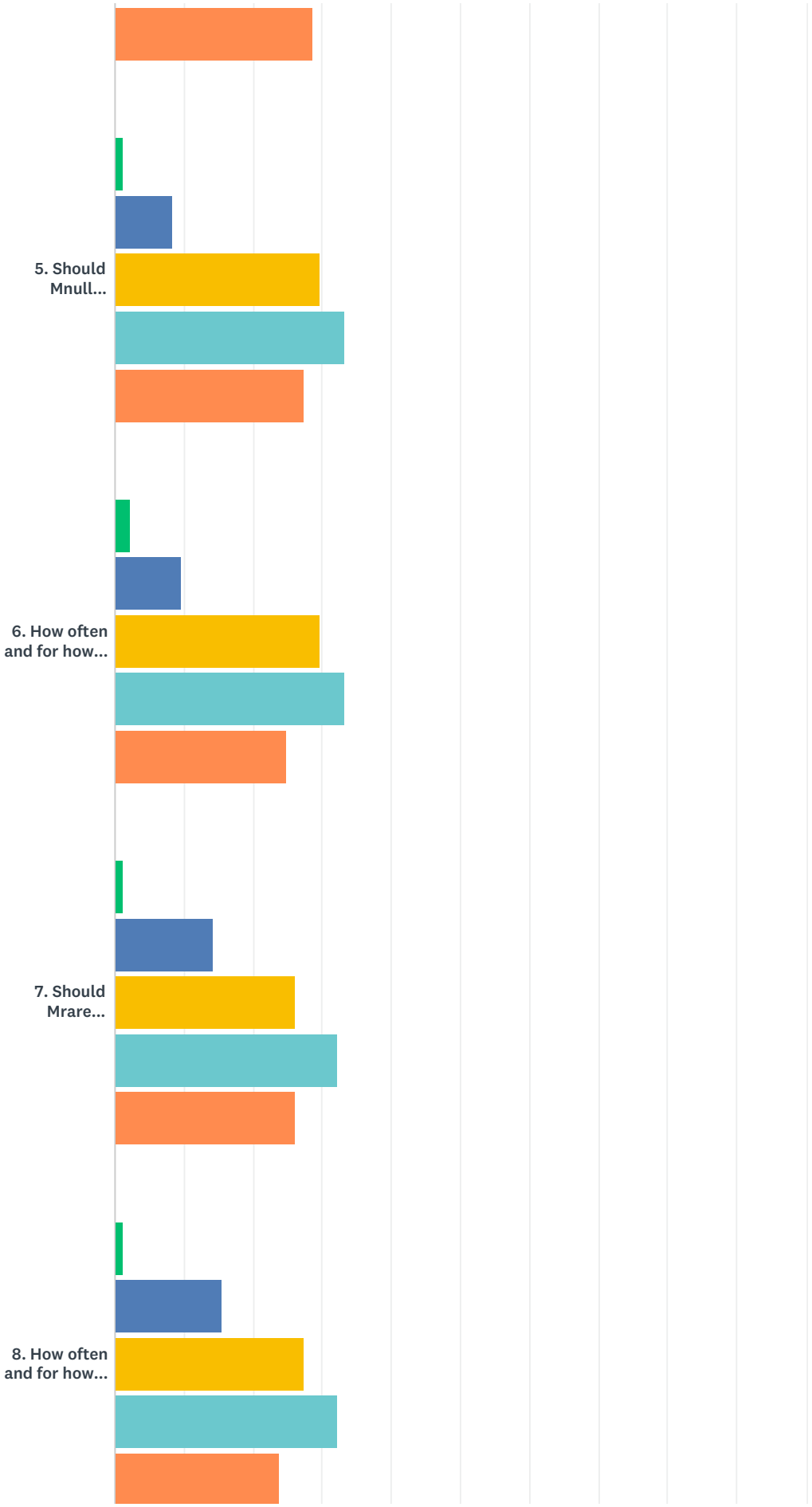
Q15 Please indicate if you have any additional research priorities that you considered necessary to include or have any further comments for the ‘Clinical manifestations‘ research area:

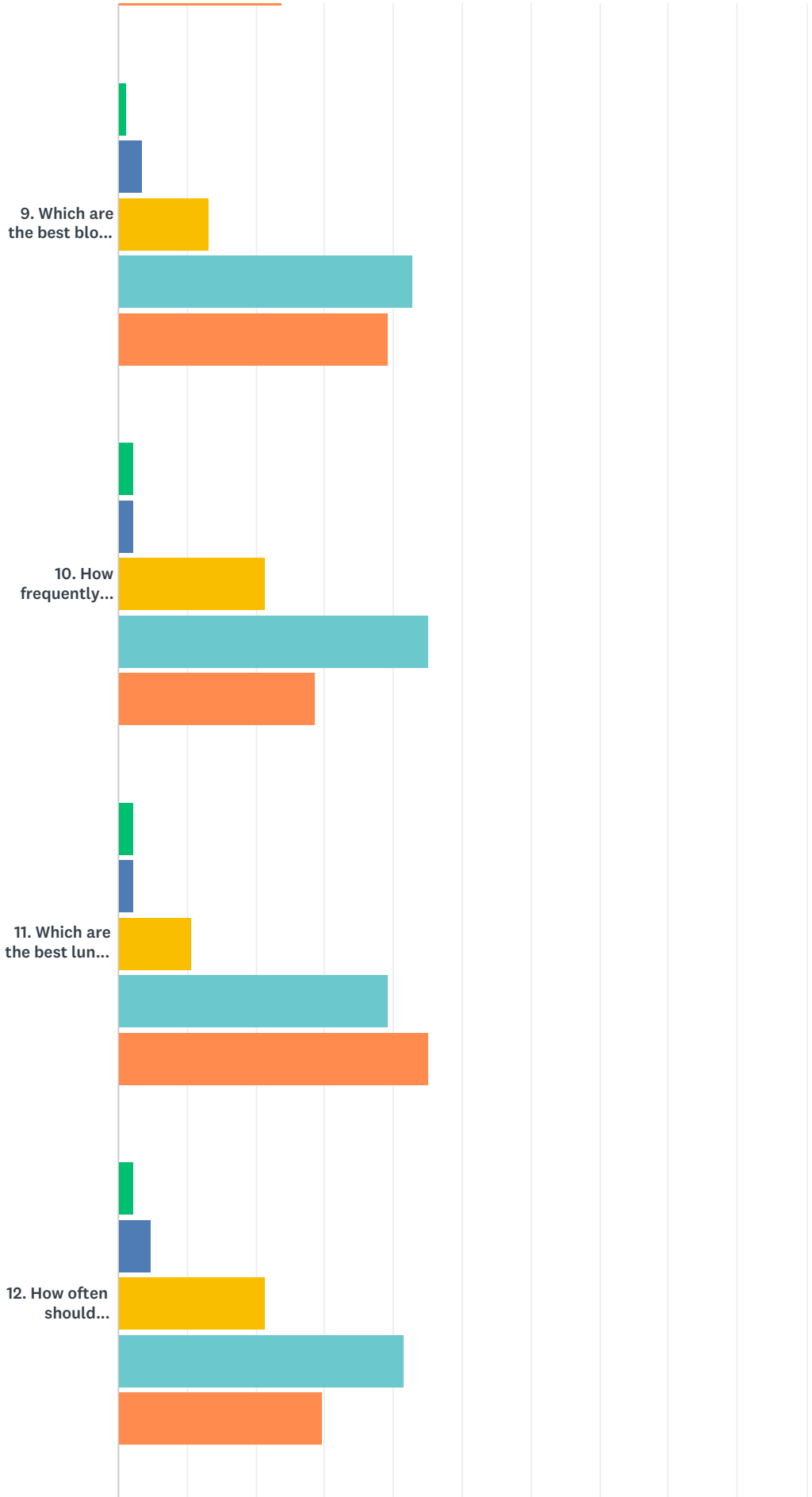
Answered: 6 Skipped: 88

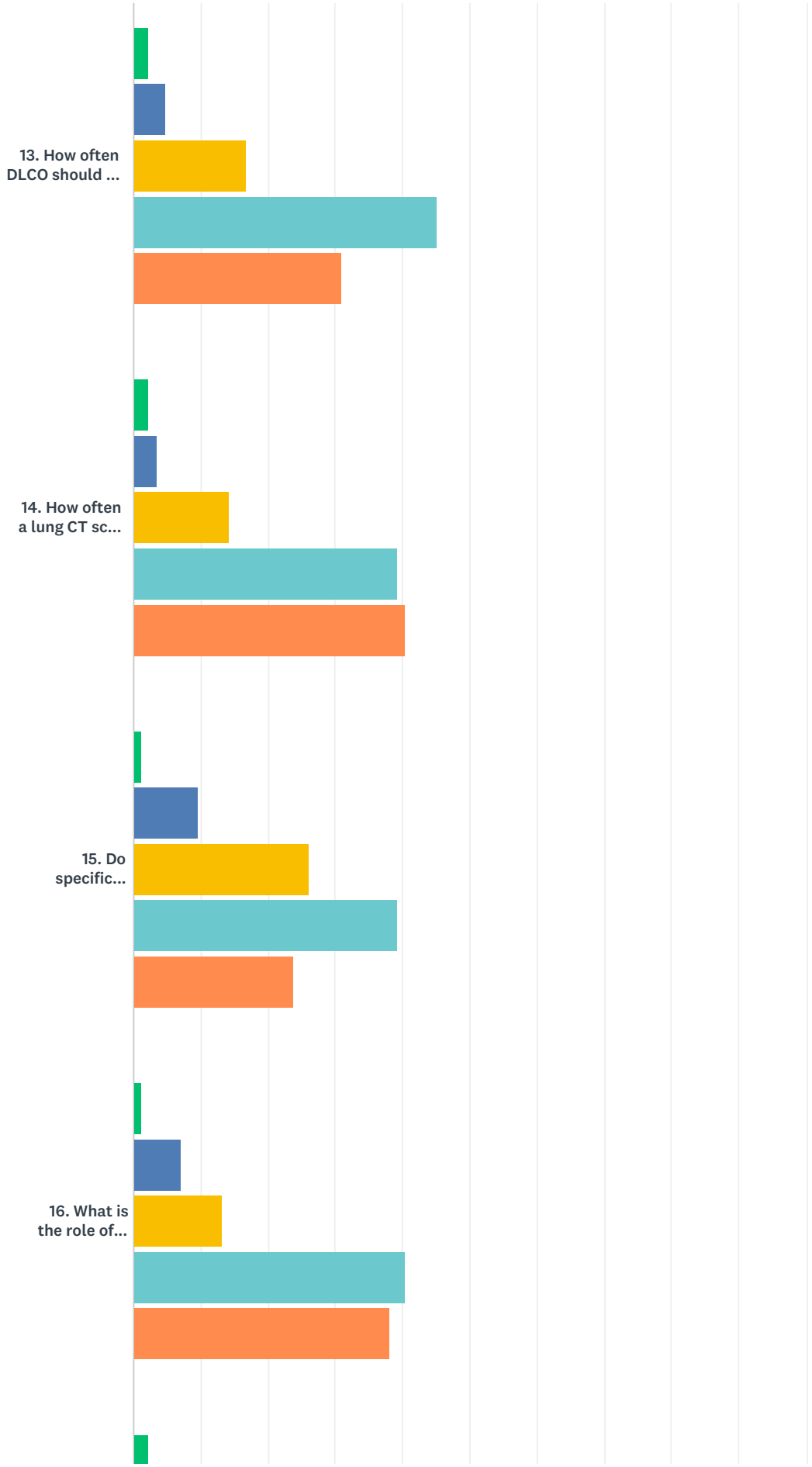
Q16 5. Outcomes and Monitoring

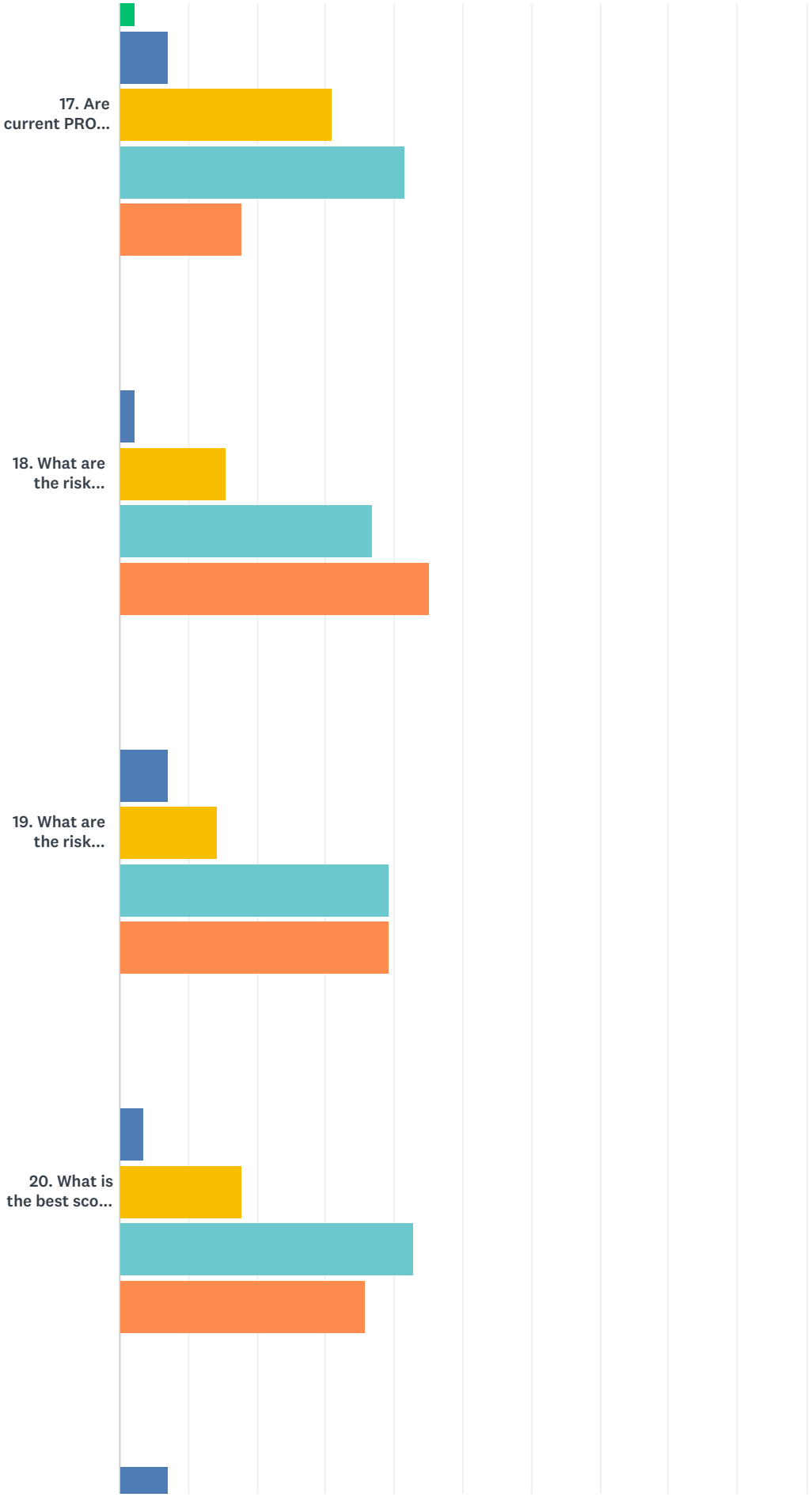
Answered: 84 Skipped: 10

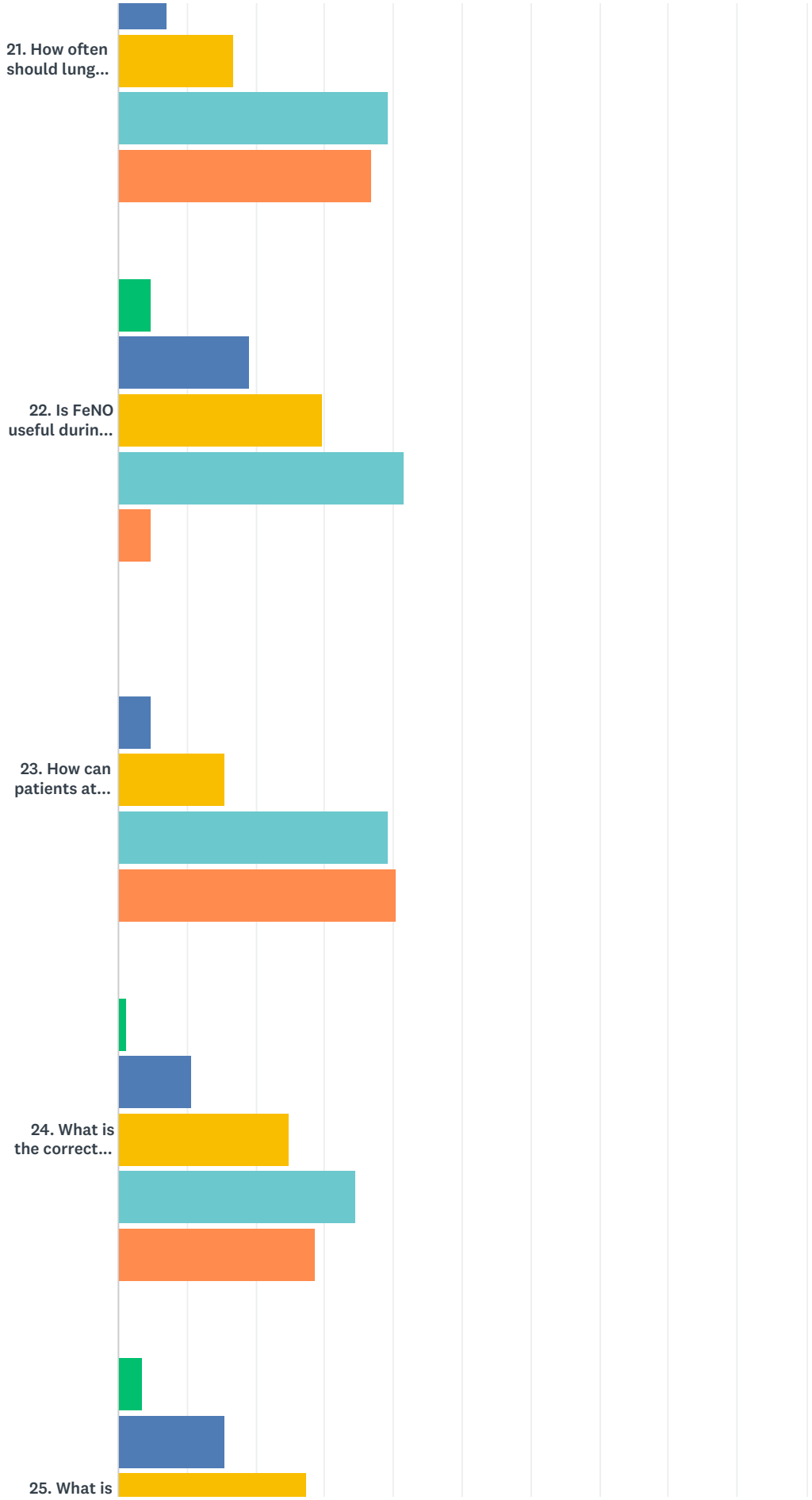


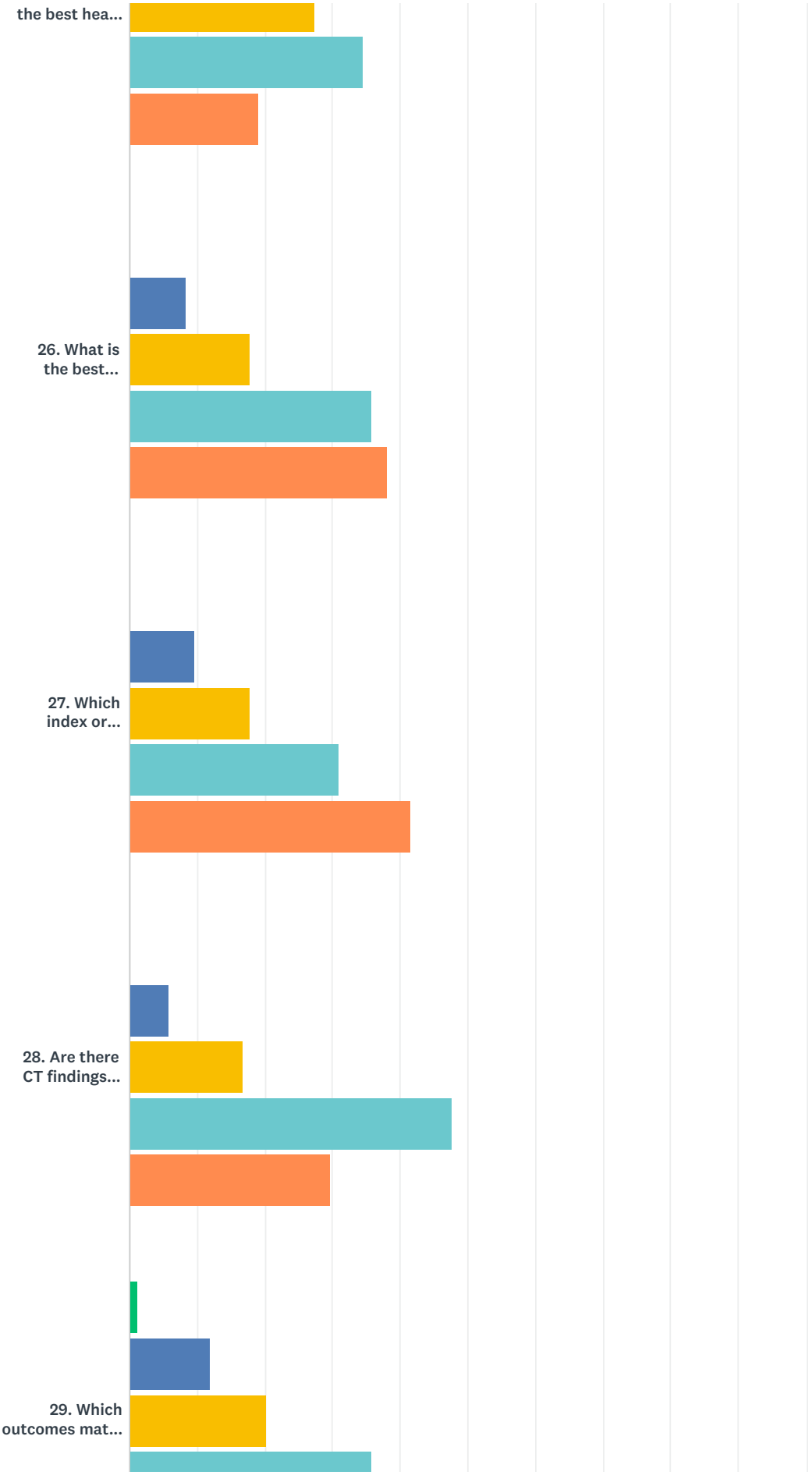

5. Should Mnull...
6. How often and for how...
7. Should Mrare...
8. How often and for how...

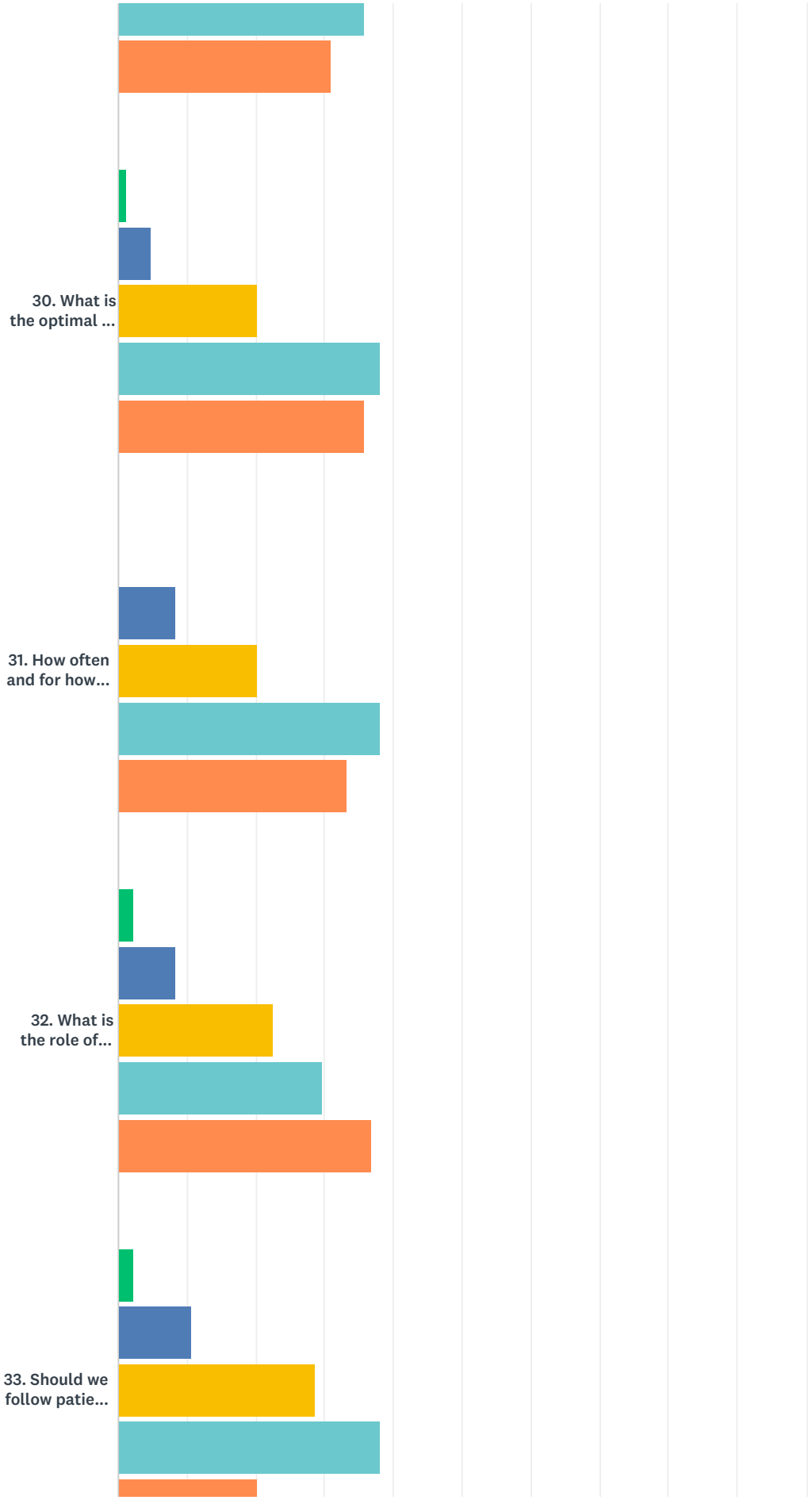

9. Which are the best blo...
10. How frequently...
11. Which are the best lun...
12. How often should...

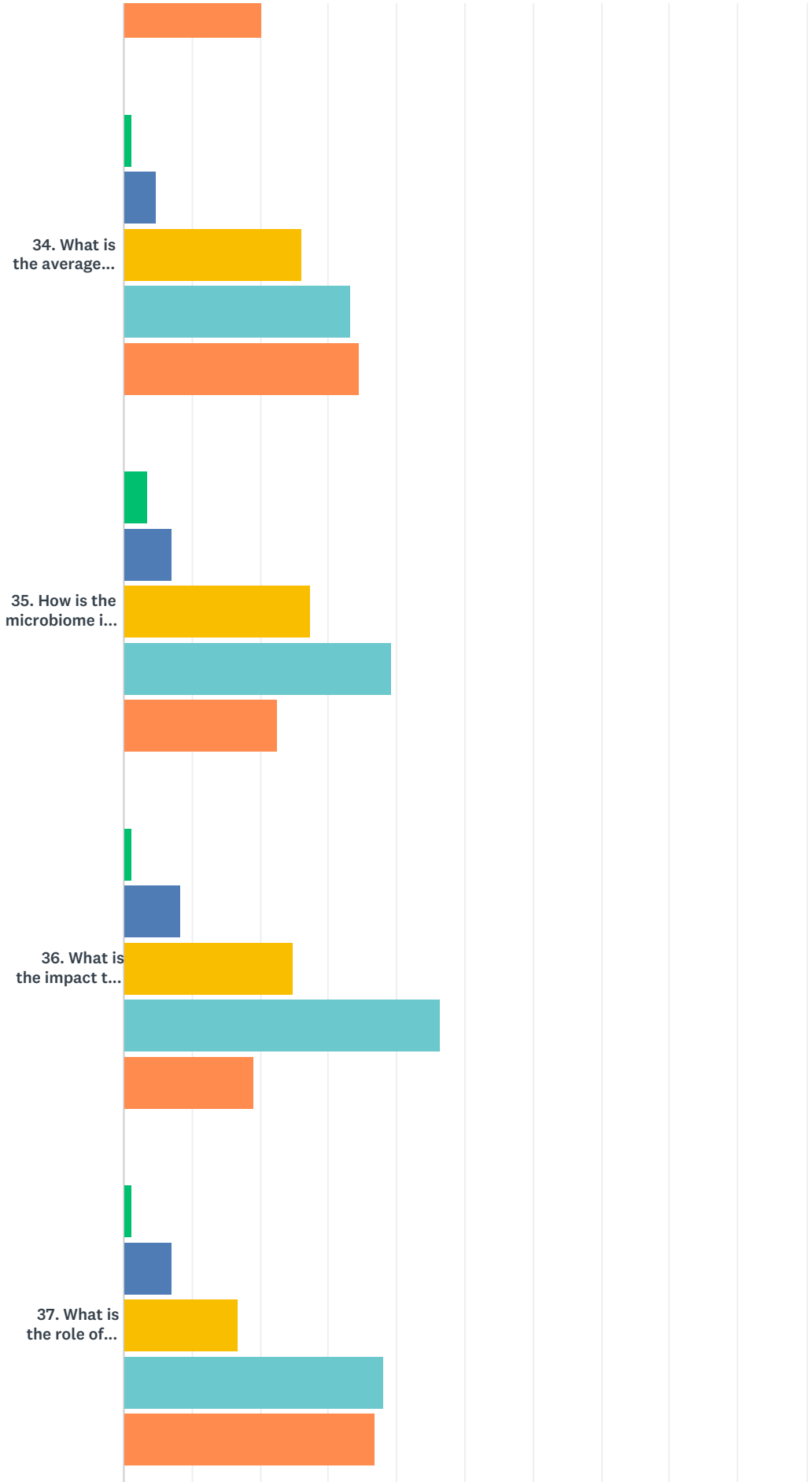

13. How often DLCO should ...
14. How often a lung CT sc...
15. Do specific...
16. What is the role of...

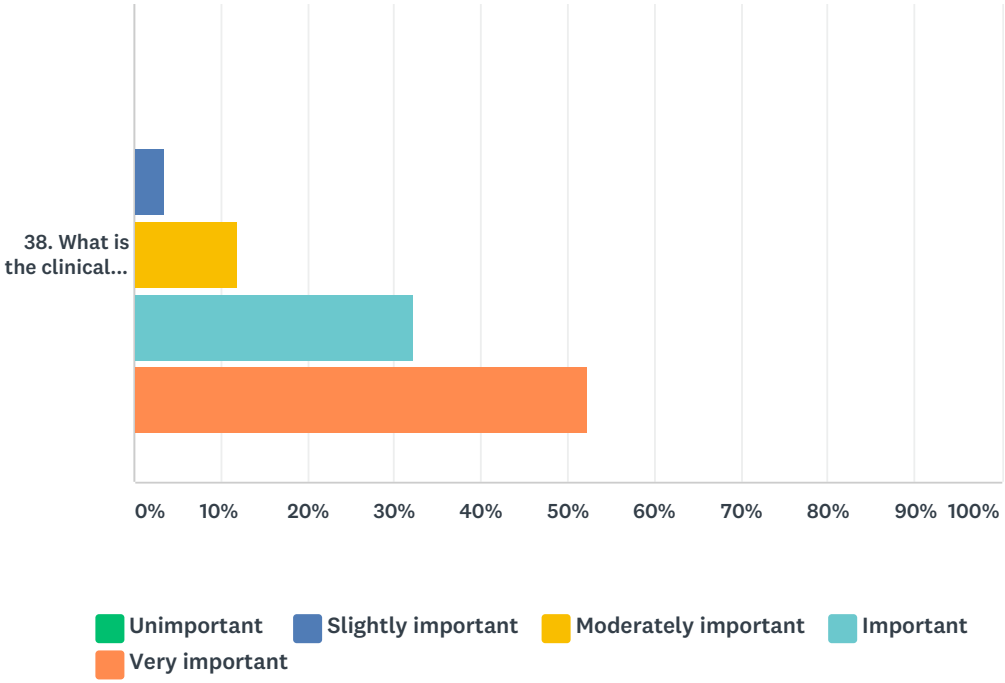

17. Are current PRO...
18. What are the risk...
19. What are the risk...
20. What is the best sco...


21. How often should lung...
22. Is FeNO useful durin...
23. How can patients at...
24. What is the correct...
25. What is


the best hea...
26. What is the best...
27. Which index or...
28. Are there CT findings...
29. Which outcomes mat...


30. What is the optimal ...
31. How often and for how...
32. What is the role of...
33. Should we follow patie...


34. What is the average...
35. How is the microbiome i...
36. What is the impact t...
37. What is the role of...



	UNIMPORTANT	SLIGHTLY IMPORTANT	MODERATELY IMPORTANT	IMPORTANT	VERY IMPORTANT	TOTAL	WEIGHTED AVERAGE
1. Should MZ individuals without disease manifestations be followed in a respiratory clinic?	3.57% 3	14.29% 12	35.71% 30	32.14% 27	14.29% 12	84	3.39
2. How often and for how long should MZ without disease be followed in respiratory clinics?	3.57% 3	14.29% 12	35.71% 30	28.57% 24	17.86% 15	84	3.43
3. Should SZ individuals without disease manifestations be followed in a respiratory clinic?	0.00% 0	5.95% 5	28.57% 24	38.10% 32	27.38% 23	84	3.87
4. How often and for how long should SZ without disease be followed in respiratory clinics?	0.00% 0	8.33% 7	26.19% 22	36.90% 31	28.57% 24	84	3.86
5. Should Mnull individuals without disease manifestations be followed in a respiratory clinic?	1.19% 1	8.33% 7	29.76% 25	33.33% 28	27.38% 23	84	3.77
6. How often and for how long should Mnull without disease be followed in respiratory clinics?	2.38% 2	9.52% 8	29.76% 25	33.33% 28	25.00% 21	84	3.69
7. Should Mrare individuals without disease manifestations be followed in a respiratory clinic?	1.19% 1	14.29% 12	26.19% 22	32.14% 27	26.19% 22	84	3.68

8. How often and for how long should Mrare without disease be followed in respiratory clinics?	1.19% 1	15.48% 13	27.38% 23	32.14% 27	23.81% 20	84	3.62
9. Which are the best blood markers for the diagnosis and follow-up of liver disease in AATD patients?	1.19% 1	3.57% 3	13.10% 11	42.86% 36	39.29% 33	84	4.15
10. How frequently should AATD patients undergo a transient elastography for the screening of liver disease?	2.38% 2	2.38% 2	21.43% 18	45.24% 38	28.57% 24	84	3.95
11. Which are the best lung function tests for the follow-up of pulmonary disease in AATD patients?	2.38% 2	2.38% 2	10.71% 9	39.29% 33	45.24% 38	84	4.23
12. How often should spirometry be performed during follow-up?	2.38% 2	4.76% 4	21.43% 18	41.67% 35	29.76% 25	84	3.92
13. How often DLCO should be performed during follow-up?	2.38% 2	4.76% 4	16.67% 14	45.24% 38	30.95% 26	84	3.98
14. How often a lung CT scan should be performed during follow-up?	2.38% 2	3.57% 3	14.29% 12	39.29% 33	40.48% 34	84	4.12
15. Do specific patient education packages, self-management plans and patients support groups improve outcomes in patients with AATD?	1.19% 1	9.52% 8	26.19% 22	39.29% 33	23.81% 20	84	3.75
16. What is the role of pulmonary rehabilitation in patients with AATD?	1.19% 1	7.14% 6	13.10% 11	40.48% 34	38.10% 32	84	4.07
17. Are current PRO used in COPD suitable for AATD individuals?	2.38% 2	7.14% 6	30.95% 26	41.67% 35	17.86% 15	84	3.65
18. What are the risk factors, other than cigarette smoking, for the development of lung disease in AATD?	0.00% 0	2.38% 2	15.48% 13	36.90% 31	45.24% 38	84	4.25
19. What are the risk factors, other than alcohol, for the development of liver disease in AATD?	0.00% 0	7.14% 6	14.29% 12	39.29% 33	39.29% 33	84	4.11

20. What is the best score to evaluate radiology severity and progression in patients with AATD?	0.00% 0	3.57% 3	17.86% 15	42.86% 36	35.71% 30	84	4.11
21. How often should lung density be measured during follow up in AATD?	0.00% 0	7.14% 6	16.67% 14	39.29% 33	36.90% 31	84	4.06
22. Is FeNO useful during follow-up in AATD?	4.76% 4	19.05% 16	29.76% 25	41.67% 35	4.76% 4	84	3.23
23. How can patients at increase risk of poor outcome or needing urgent treatment be identified?	0.00% 0	4.76% 4	15.48% 13	39.29% 33	40.48% 34	84	4.15
24. What is the correct threshold of AAT serum level for detecting heterozygous carriers?	1.19% 1	10.71% 9	25.00% 21	34.52% 29	28.57% 24	84	3.79
25. What is the best health status questionnaire to evaluate AATD patients?	3.57% 3	15.48% 13	27.38% 23	34.52% 29	19.05% 16	84	3.50
26. What is the best prognostic score in AATD?	0.00% 0	8.33% 7	17.86% 15	35.71% 30	38.10% 32	84	4.04
27. Which index or indices best stratify AATD patients for the purpose of determining disease severity or recommending treatment?	0.00% 0	9.52% 8	17.86% 15	30.95% 26	41.67% 35	84	4.05
28. Are there CT findings associated with clinically significant features and differential responses to treatment in AATD?	0.00% 0	5.95% 5	16.67% 14	47.62% 40	29.76% 25	84	4.01
29. Which outcomes matter most to patients and, therefore, are truly patient-centered outcomes in AATD?	1.19% 1	11.90% 10	20.24% 17	35.71% 30	30.95% 26	84	3.83
30. What is the optimal CT protocol and quantification method in AATD patients?	1.19% 1	4.76% 4	20.24% 17	38.10% 32	35.71% 30	84	4.02
31. How often and for how long should deficient individuals without clinical manifestations be followed?	0.00% 0	8.33% 7	20.24% 17	38.10% 32	33.33% 28	84	3.96

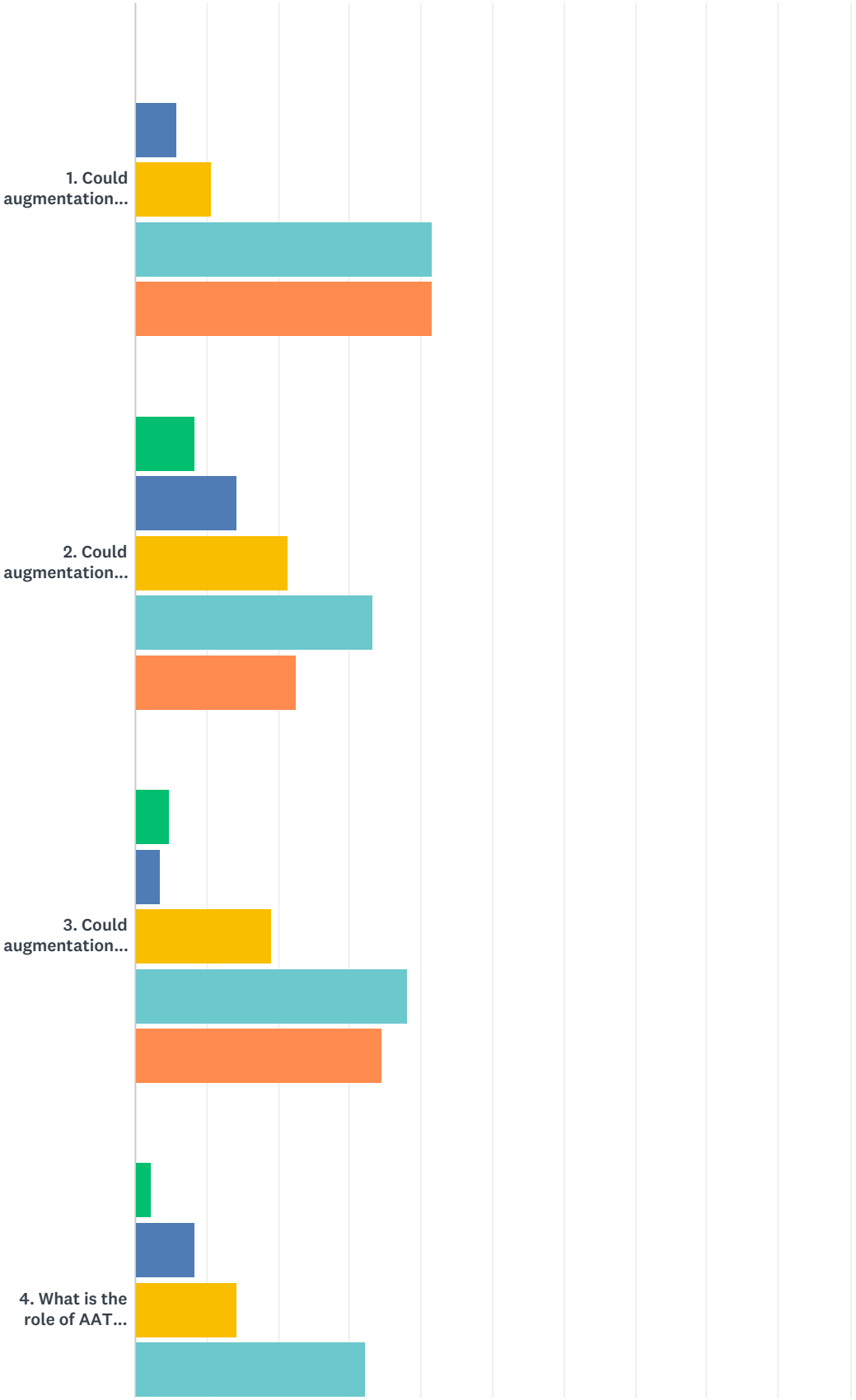
32. What is the role of lung transplant in patients with AATD?	2.38% 2	8.33% 7	22.62% 19	29.76% 25	36.90% 31	84	3.90
33. Should we follow patients with AATD without lung disease after a liver transplant and for how long?	2.38% 2	10.71% 9	28.57% 24	38.10% 32	20.24% 17	84	3.63
34. What is the average lung function decline for MZ, SZ and SS patients?	1.19% 1	4.76% 4	26.19% 22	33.33% 28	34.52% 29	84	3.95
35. How is the microbiome in AATD patients, and it is different among phenotypes and compared to non AATD COPD?	3.57% 3	7.14% 6	27.38% 23	39.29% 33	22.62% 19	84	3.70
36. What is the impact that viral infections have on the evolution of AATD?	1.19% 1	8.33% 7	25.00% 21	46.43% 39	19.05% 16	84	3.74
37. What is the role of gene therapy in AATD?	1.19% 1	7.14% 6	16.67% 14	38.10% 32	36.90% 31	84	4.02
38. What is the clinically valid definition of fast decliner, what is advisable observation period?	0.00% 0	3.57% 3	11.90% 10	32.14% 27	52.38% 44	84	4.33

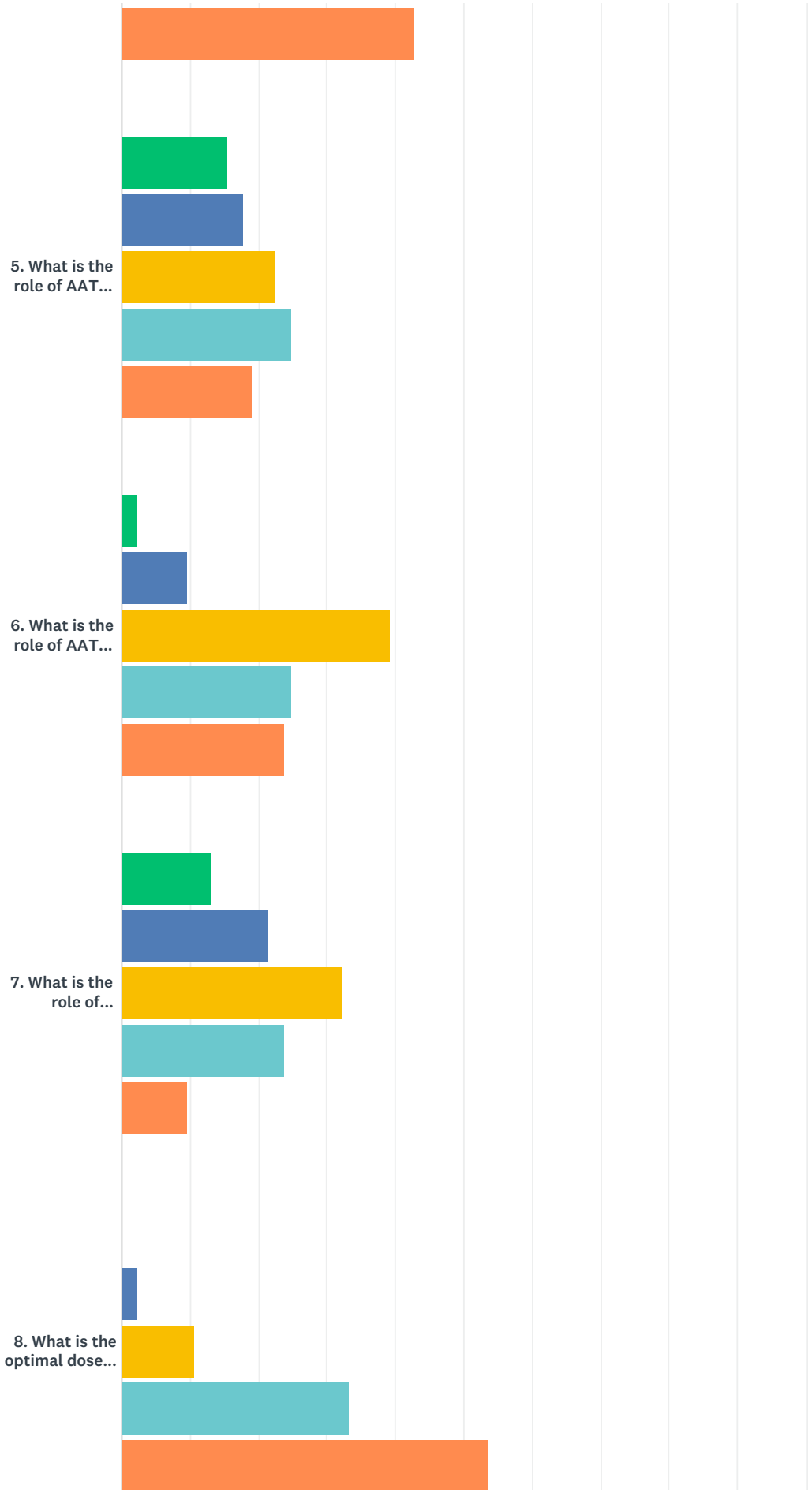
Q17 Please indicate if you have any additional research priorities that you considered necessary to include or have any further comments for the ‘Outcomes and Monitoring‘ research area:

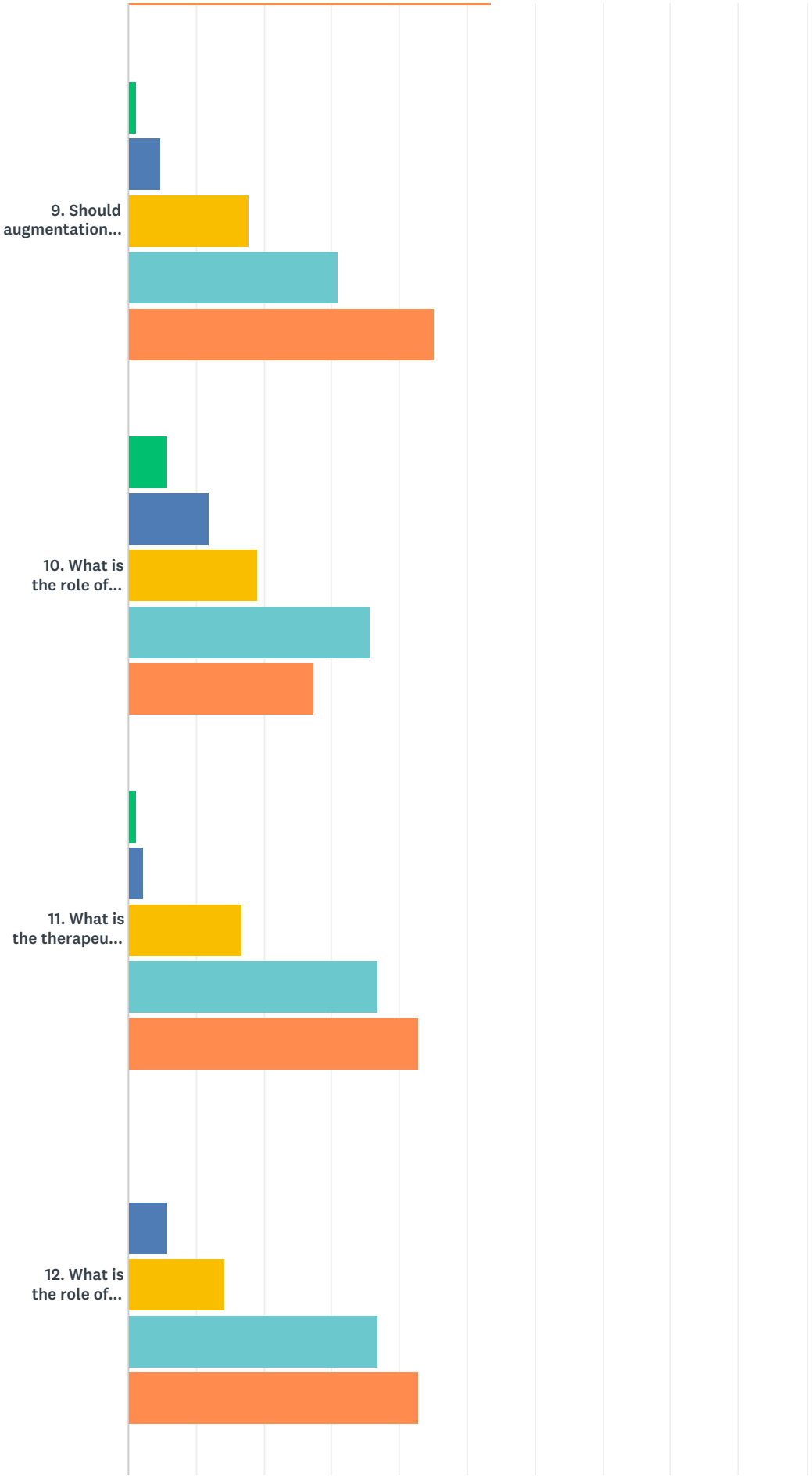
Answered: 6 Skipped: 88

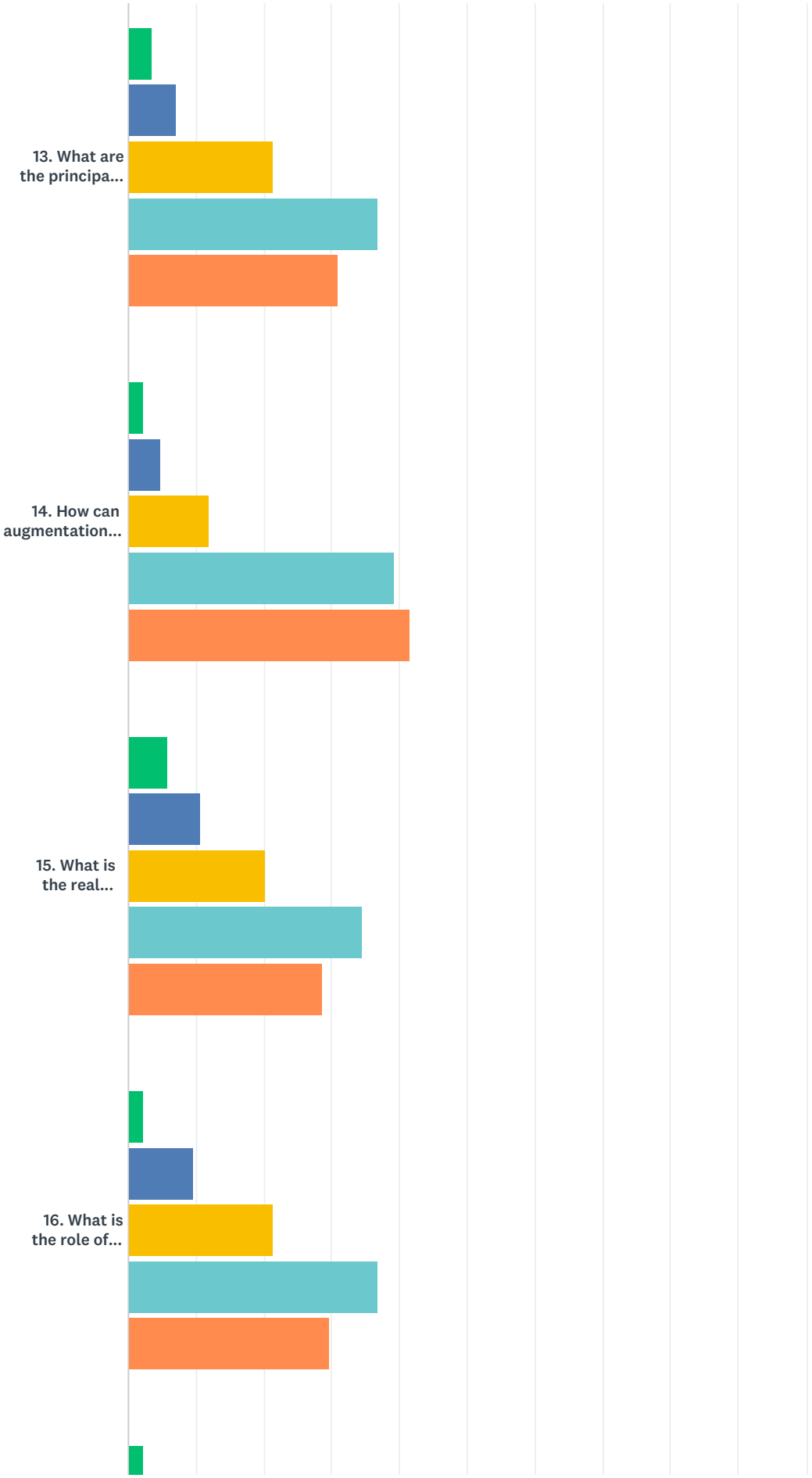
Q18 6. Augmentation therapy

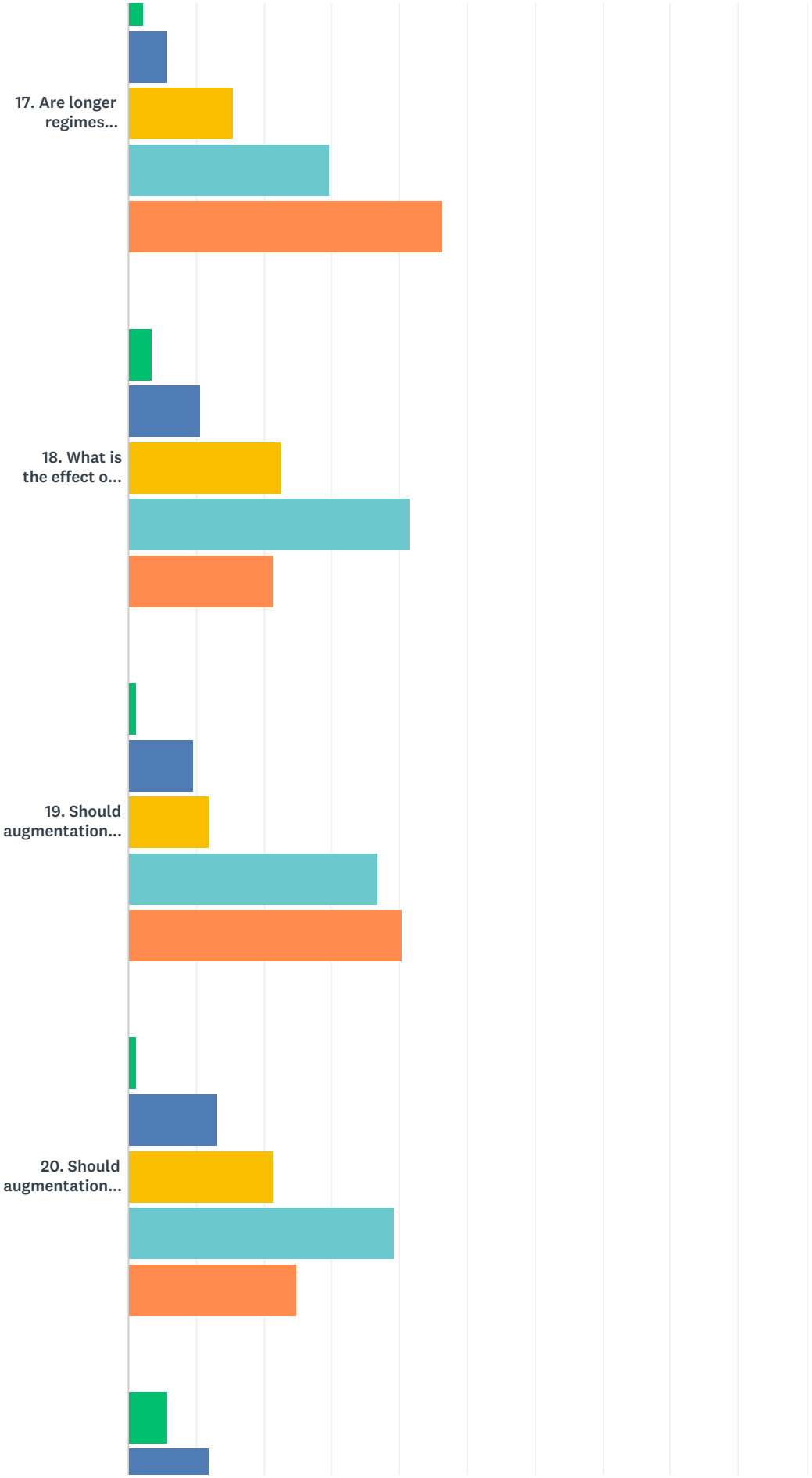
Answered: 84 Skipped: 10

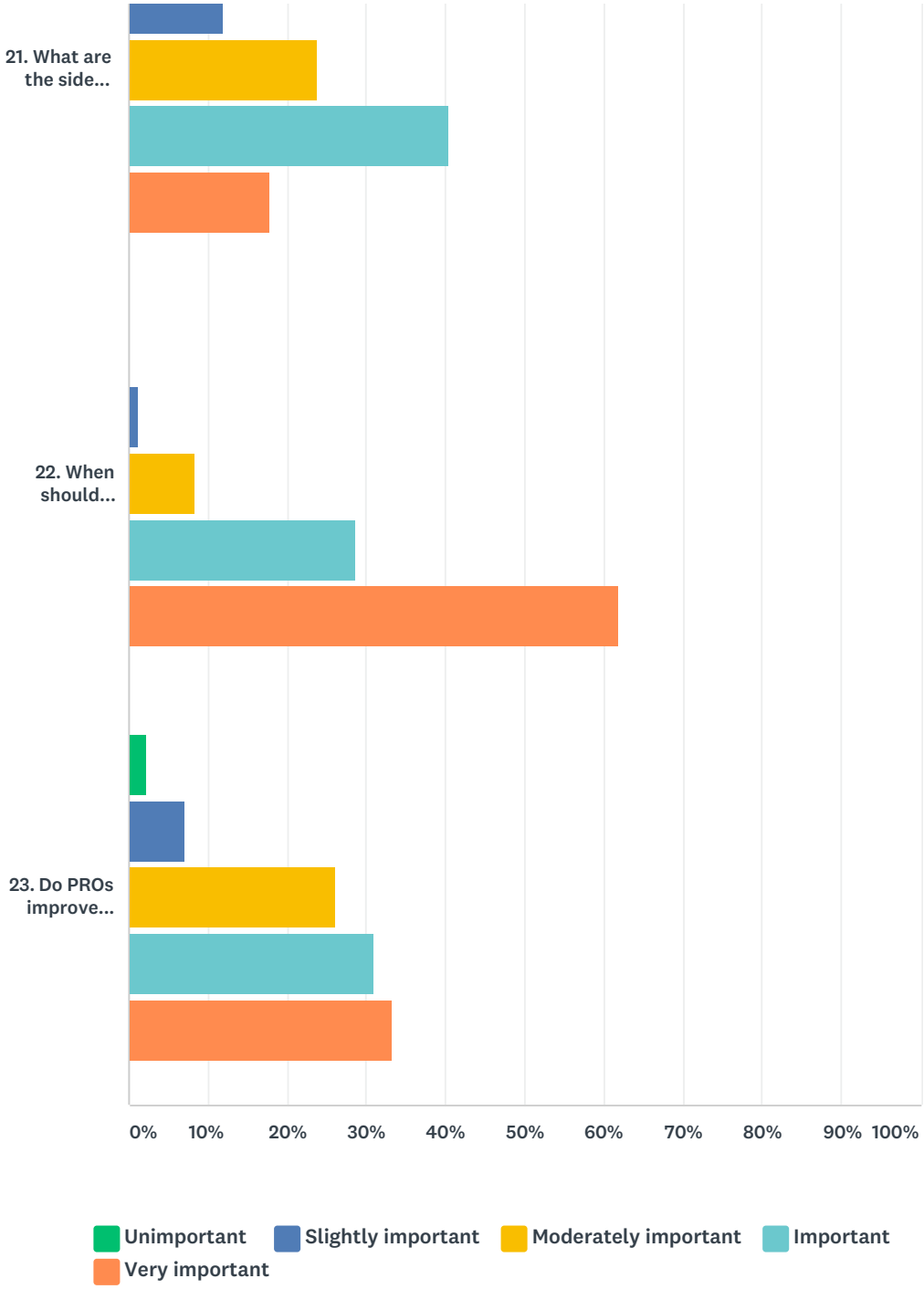



5. What is the role of AAT...
6. What is the role of AAT...
7. What is the role of...
8. What is the optimal dose...


9. Should augmentation...
10. What is the role of...
11. What is the therapeu...
12. What is the role of...


13. What are the principa...
14. How can augmentation...
15. What is the real...
16. What is the role of...


17. Are longer regimes...
18. What is the effect o...
19. Should augmentation...
20. Should augmentation...



	UNIMPORTANT	SLIGHTLY IMPORTANT	MODERATELY IMPORTANT	IMPORTANT	VERY IMPORTANT	TOTAL	WEIGHTED AVERAGE
1. Could augmentation therapy be effective in other phenotypes/genotypes with low levels such as SZ?	0.00% 0	5.95% 5	10.71% 9	41.67% 35	41.67% 35	84	4.19
2. Could augmentation therapy be effective in MZ patients?	8.33% 7	14.29% 12	21.43% 18	33.33% 28	22.62% 19	84	3.48

3. Could augmentation therapy be effective in rare phenotypes/genotypes with normal levels but low AAT enzymatic activity (PiF?)	4.76% 4	3.57% 3	19.05% 16	38.10% 32	34.52% 29	84	3.94
4. What is the role of AAT augmentation therapy after lung transplantation?	2.38% 2	8.33% 7	14.29% 12	32.14% 27	42.86% 36	84	4.05
5. What is the role of AAT augmentation therapy after liver transplantation?	15.48% 13	17.86% 15	22.62% 19	25.00% 21	19.05% 16	84	3.14
6. What is the role of AAT augmentation therapy for panniculitis, in patients with AATD?	2.38% 2	9.52% 8	39.29% 33	25.00% 21	23.81% 20	84	3.58
7. What is the role of augmentation therapy for fibromyalgia in patients with AATD?	13.10% 11	21.43% 18	32.14% 27	23.81% 20	9.52% 8	84	2.95
8. What is the optimal dose regimen (dose and frequency of administration) of augmentation therapy?	0.00% 0	2.38% 2	10.71% 9	33.33% 28	53.57% 45	84	4.38
9. Should augmentation therapy be considered in PI*ZZ patients with bronchiectasis without emphysema?	1.19% 1	4.76% 4	17.86% 15	30.95% 26	45.24% 38	84	4.14
10. What is the role of augmentation therapy in AATD asthmatic patients?	5.95% 5	11.90% 10	19.05% 16	35.71% 30	27.38% 23	84	3.67
11. What is the therapeutic efficacy of aerosol AAT preparation?	1.19% 1	2.38% 2	16.67% 14	36.90% 31	42.86% 36	84	4.18
12. What is the role of augmentation therapy for reduction of exacerbations frequency and severity?	0.00% 0	5.95% 5	14.29% 12	36.90% 31	42.86% 36	84	4.17
13. What are the principal barriers for unequal reimbursement policies for AAT augmentation therapy across Europe?	3.57% 3	7.14% 6	21.43% 18	36.90% 31	30.95% 26	84	3.85
14. How can augmentation therapy be accessible to all patients across Europe?	2.38% 2	4.76% 4	11.90% 10	39.29% 33	41.67% 35	84	4.13

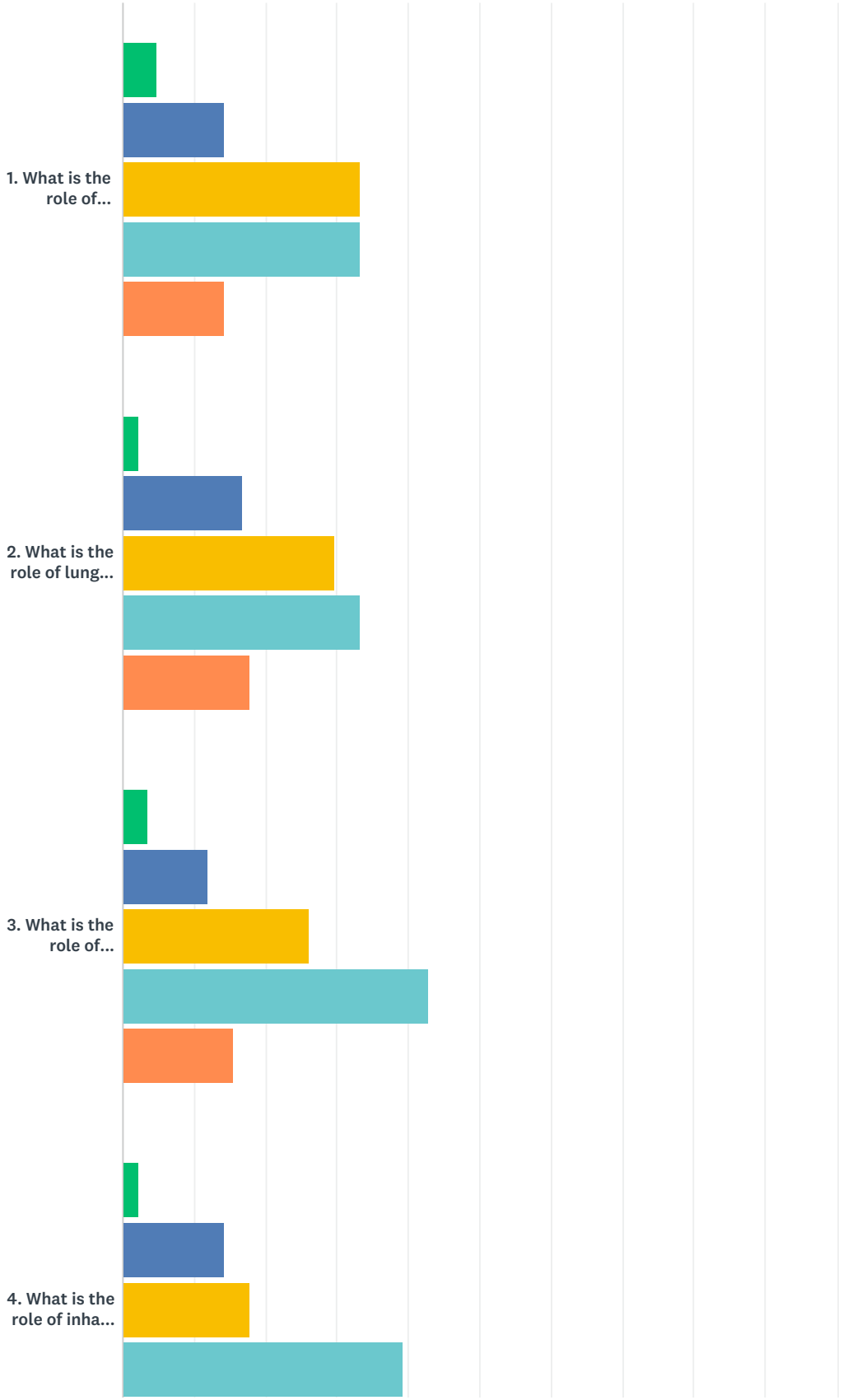
15. What is the real prevalence of adverse effects of augmentation therapy?	5.95% 5	10.71% 9	20.24% 17	34.52% 29	28.57% 24	84	3.69
16. What is the role of home intravenous augmentation therapy?	2.38% 2	9.52% 8	21.43% 18	36.90% 31	29.76% 25	84	3.82
17. Are longer regimes (biweekly and every 3 weeks) really equivalent to weekly augmentation therapy?	2.38% 2	5.95% 5	15.48% 13	29.76% 25	46.43% 39	84	4.12
18. What is the effect of the discontinuation of augmentation therapy during holidays of hospital admissions?	3.57% 3	10.71% 9	22.62% 19	41.67% 35	21.43% 18	84	3.67
19. Should augmentation therapy be administered in patients with emphysema with preserved spirometry?	1.19% 1	9.52% 8	11.90% 10	36.90% 31	40.48% 34	84	4.06
20. Should augmentation therapy be administered in a home setting?	1.19% 1	13.10% 11	21.43% 18	39.29% 33	25.00% 21	84	3.74
21. What are the side effects of augmentation therapy?	5.95% 5	11.90% 10	23.81% 20	40.48% 34	17.86% 15	84	3.52
22. When should augmentation therapy be initiated?	0.00% 0	1.19% 1	8.33% 7	28.57% 24	61.90% 52	84	4.51
23. Do PROs improve (deteriote significantly less) under augmentation therapy?	2.38% 2	7.14% 6	26.19% 22	30.95% 26	33.33% 28	84	3.86

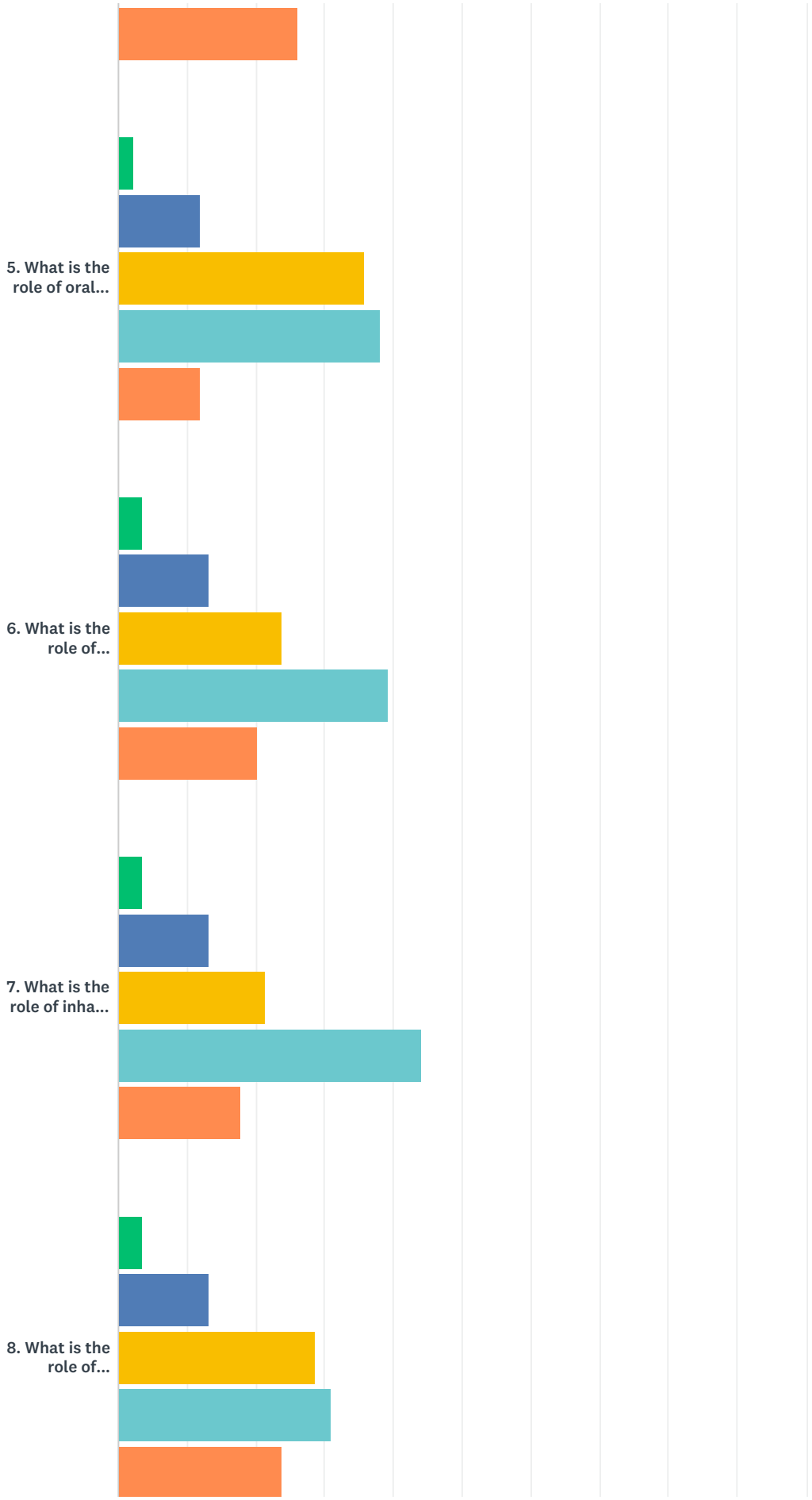
Q19 Please indicate if you have any additional research priorities that you considered necessary to include or have any further comments for the ‘Augmentation therapy‘ research area:

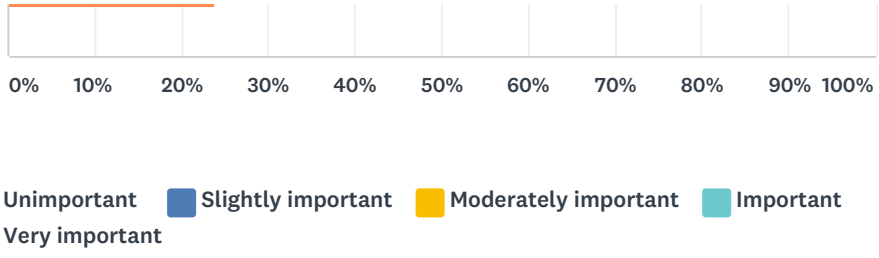
Answered: 6 Skipped: 88

Q20 7. Other treatments / AATD therapies

Answered: 84 Skipped: 10




5. What is the role of oral...
6. What is the role of...
7. What is the role of inha...
8. What is the role of...



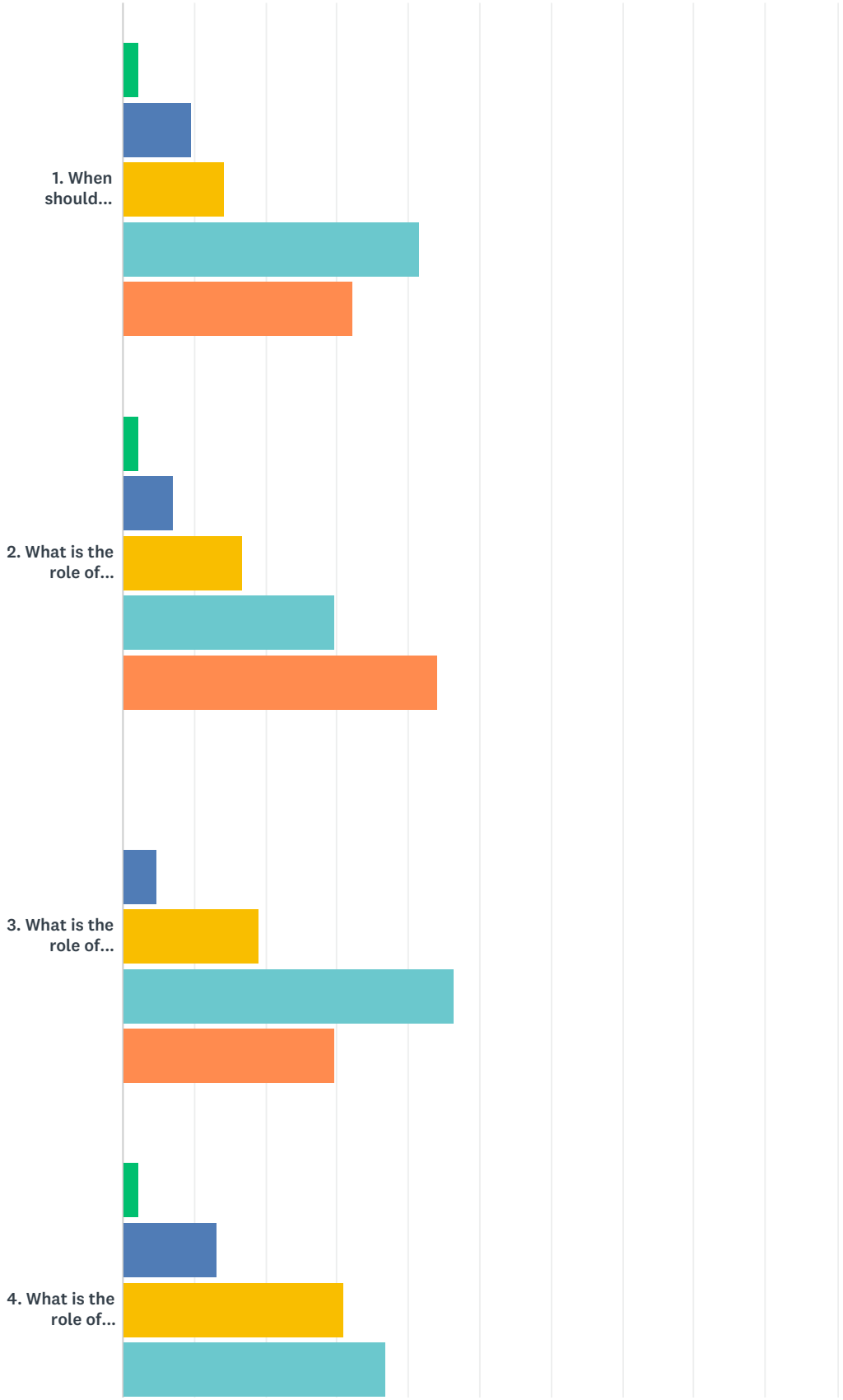
	UNIMPORTANT	SLIGHTLY IMPORTANT	MODERATELY IMPORTANT	IMPORTANT	VERY IMPORTANT	TOTAL	WEIGHTED AVERAGE
1. What is the role of endoscopic therapy in AATD?	4.76% 4	14.29% 12	33.33% 28	33.33% 28	14.29% 12	84	3.38
2. What is the role of lung volume reduction surgery in AATD?	2.38% 2	16.67% 14	29.76% 25	33.33% 28	17.86% 15	84	3.48
3. What is the role of systemic steroids during an exacerbation of AATD?	3.57% 3	11.90% 10	26.19% 22	42.86% 36	15.48% 13	84	3.55
4. What is the role of inhaled steroids in patients with AATD?	2.38% 2	14.29% 12	17.86% 15	39.29% 33	26.19% 22	84	3.73
5. What is the role of oral mucolytics in patients with AATD?	2.38% 2	11.90% 10	35.71% 30	38.10% 32	11.90% 10	84	3.45
6. What is the role of long-term antibiotic therapy in AATD patients?	3.57% 3	13.10% 11	23.81% 20	39.29% 33	20.24% 17	84	3.60
7. What is the role of inhaled antibiotics in patients with AATD and clinical manifestations?	3.57% 3	13.10% 11	21.43% 18	44.05% 37	17.86% 15	84	3.60
8. What is the role of biologics for the management of AATD?	3.57% 3	13.10% 11	28.57% 24	30.95% 26	23.81% 20	84	3.58

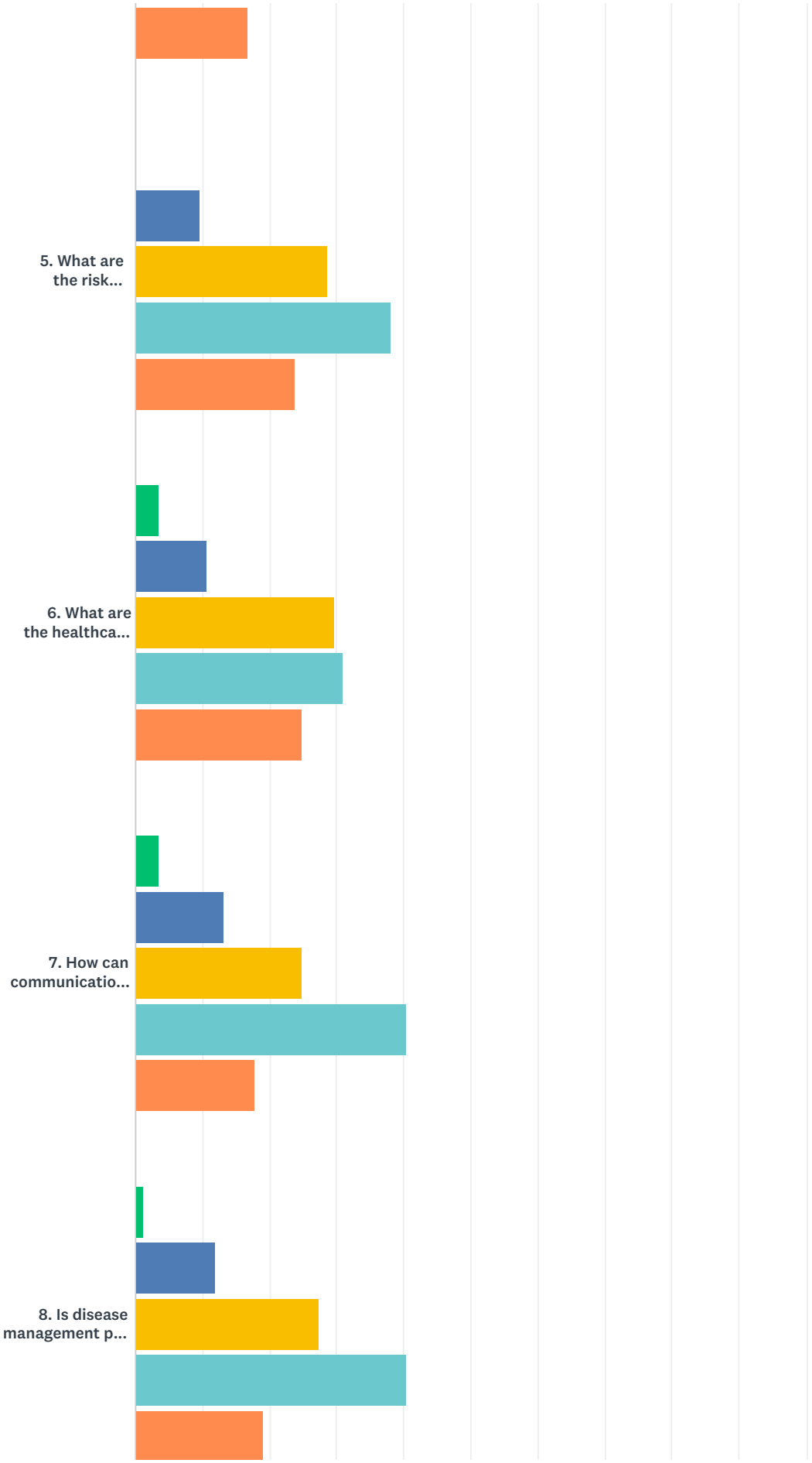
Q21 Please indicate if you have any additional research priorities that you considered necessary to include or have any further comments for the ‘Other treatments/AATD therapies‘ research area:

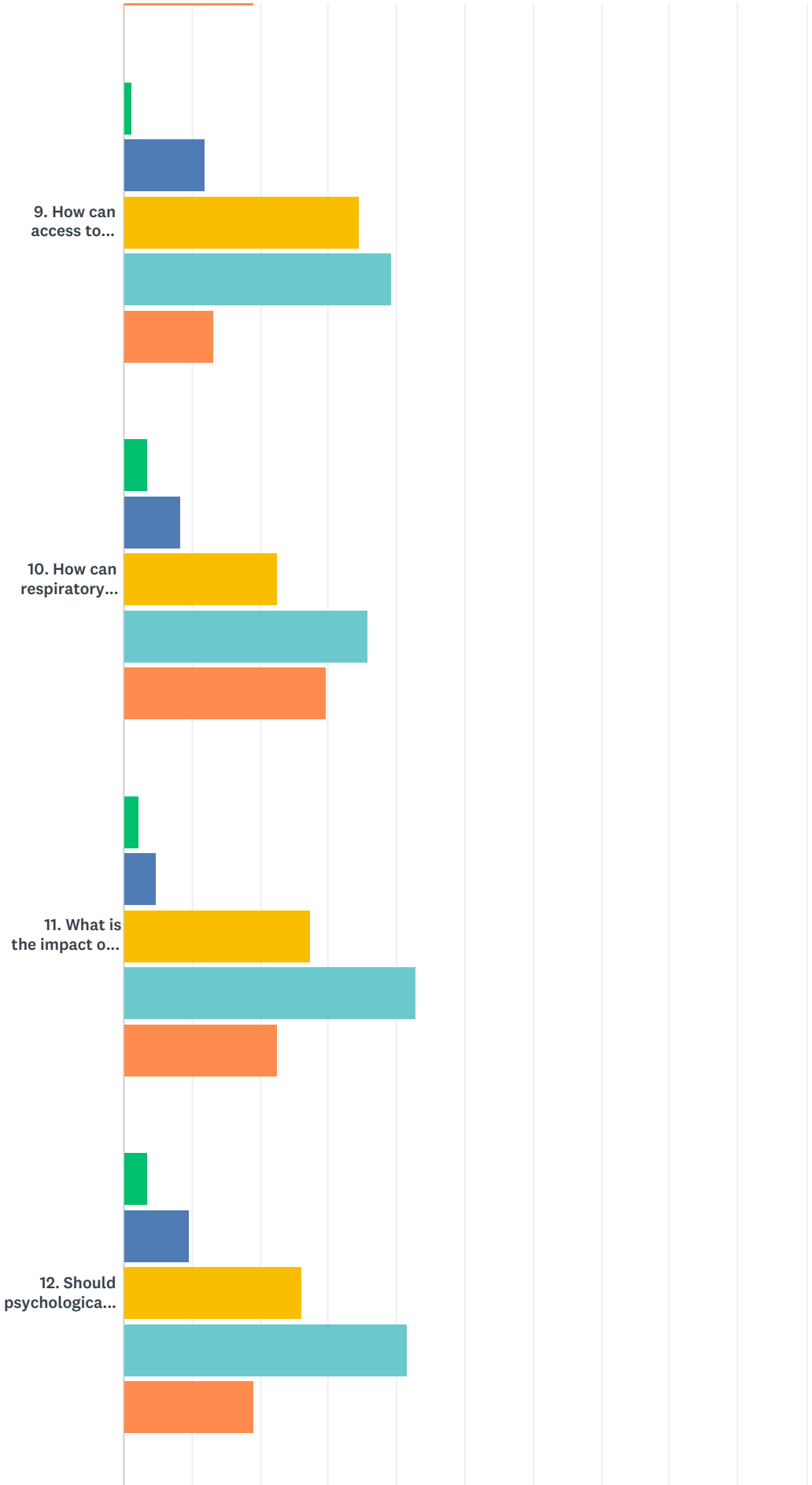
Answered: 5 Skipped: 89

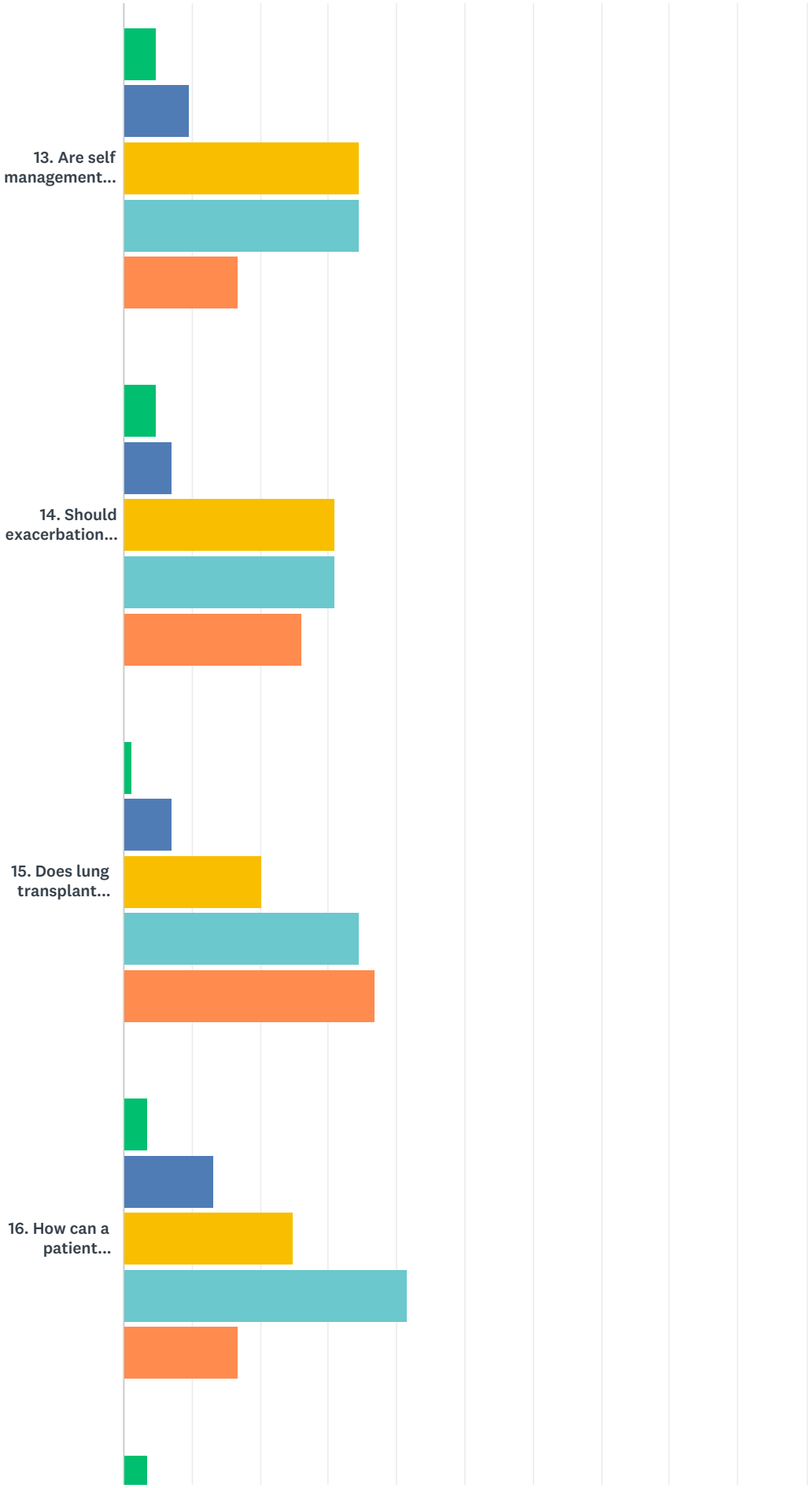
Q22 8. Other non pharmacological interventions

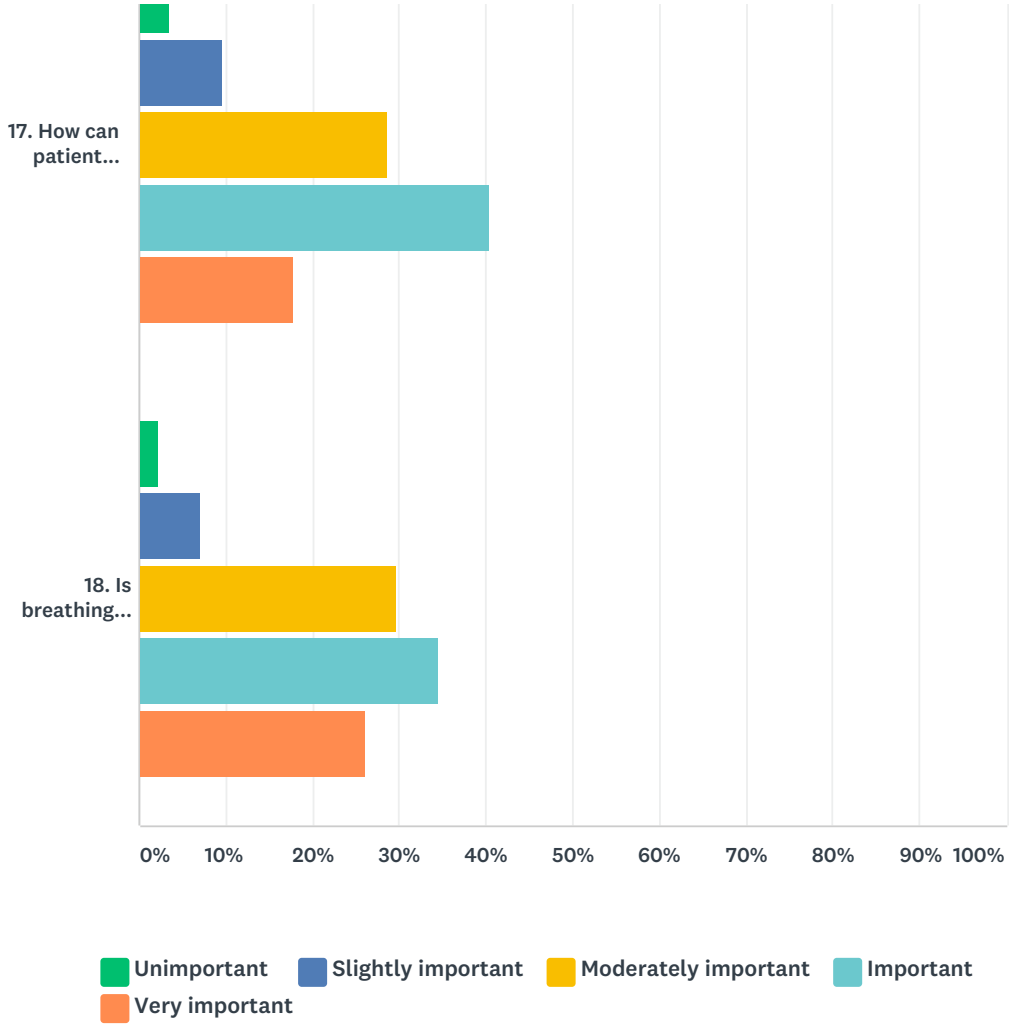
Answered: 84 Skipped: 10




5. What are the risk...
6. What are the healthca...
7. How can communicatio...
8. Is disease management p...


9. How can access to...
10. How can respiratory...
11. What is the impact o...
12. Should psychologica...


13. Are self management...
14. Should exacerbation...
15. Does lung transplant...
16. How can a patient...



	UNIMPORTANT	SLIGHTLY IMPORTANT	MODERATELY IMPORTANT	IMPORTANT	VERY IMPORTANT	TOTAL	WEIGHTED AVERAGE
1. When should pulmonary rehabilitation be offered/started in AATD patients?	2.38% 2	9.52% 8	14.29% 12	41.67% 35	32.14% 27	84	3.92
2. What is the role of pulmonary rehabilitation in AATD?	2.38% 2	7.14% 6	16.67% 14	29.76% 25	44.05% 37	84	4.06
3. What is the role of environmental and workplace avoidance of exposure, for lung disease in AATD patients?	0.00% 0	4.76% 4	19.05% 16	46.43% 39	29.76% 25	84	4.01
4. What is the role of environmental avoidance of exposure, for liver disease in AATD patients?	2.38% 2	13.10% 11	30.95% 26	36.90% 31	16.67% 14	84	3.52
5. What are the risk factors that should be avoided in AATD patients with liver disease?	0.00% 0	9.52% 8	28.57% 24	38.10% 32	23.81% 20	84	3.76

6. What are the healthcare costs of AATD management across Europe?	3.57% 3	10.71% 9	29.76% 25	30.95% 26	25.00% 21	84	3.63
7. How can communication between healthcare professionals and each patient be optimized to improve self-management?	3.57% 3	13.10% 11	25.00% 21	40.48% 34	17.86% 15	84	3.56
8. Is disease management plan agreed with the patient?	1.19% 1	11.90% 10	27.38% 23	40.48% 34	19.05% 16	84	3.64
9. How can access to healthcare professionals improve AATD management and control of the disease?	1.19% 1	11.90% 10	34.52% 29	39.29% 33	13.10% 11	84	3.51
10. How can respiratory rehabilitation be accessible to all patients across Europe?	3.57% 3	8.33% 7	22.62% 19	35.71% 30	29.76% 25	84	3.80
11. What is the impact of diagnosis and treatment of comorbidities in AATD patients?	2.38% 2	4.76% 4	27.38% 23	42.86% 36	22.62% 19	84	3.79
12. Should psychological support be offered to AATD patients?	3.57% 3	9.52% 8	26.19% 22	41.67% 35	19.05% 16	84	3.63
13. Are self management interventions effective in AATD patients?	4.76% 4	9.52% 8	34.52% 29	34.52% 29	16.67% 14	84	3.49
14. Should exacerbation action plans be recommended for all AARD patients?	4.76% 4	7.14% 6	30.95% 26	30.95% 26	26.19% 22	84	3.67
15. Does lung transplant increase survival in AATD patients?	1.19% 1	7.14% 6	20.24% 17	34.52% 29	36.90% 31	84	3.99
16. How can a patient organisation/self-help group support the patient?	3.57% 3	13.10% 11	25.00% 21	41.67% 35	16.67% 14	84	3.55
17. How can patient organisations and professionals network better?	3.57% 3	9.52% 8	28.57% 24	40.48% 34	17.86% 15	84	3.60
18. Is breathing training/physiotherapy useful for patients with AATD?	2.38% 2	7.14% 6	29.76% 25	34.52% 29	26.19% 22	84	3.75

Q23 Please indicate if you have any additional research priorities that you considered necessary to include or have any further comments for the ‘Other non pharmacological interventions‘ research area:

Answered: 6 Skipped: 88

Q24 Do you have any further comments regarding this survey or regarding the different research priorities in the field of AATD as whole?

Answered: 11 Skipped: 83

Alpha-1 antitrypsin deficiency (AATD)
Patient survey

EARCO CRC

Final report

January 2020

Contents

Introduction

This survey is part of the scope of work led by EARCO (European Alpha-1 Research Collaboration), a Clinical Research Collaboration (CRC) of the European Respiratory Society. EARCO aims to facilitate multi-disciplinary collaborative research in Alpha-1 antitrypsin deficiency (AATD).

The survey asked people with AATD, and their family members and caregivers, to tell us what we should be looking at to provide answers to the challenges of care, treatment and living with AATD. The survey questions were developed by EARCO members including AATD patient representatives and the European Lung Foundation (ELF) and the survey was provided in 9 languages: English, Dutch, French, German, Italian, Polish, Portuguese, Serbian and Spanish. The survey was online for four weeks during November/December 2019 and promoted through the networks/social media of Alpha-1 Global, Alpha-1 patient organisations/groups, ELF, ERS and members of the CRC.

This report has been compiled by ELF staff based on the survey findings.

Short summary of survey results

More than half of respondents were diagnosed by a respiratory specialist (56%) with the most likely cause for diagnosis being COPD (32%) followed by family testing (17%). Many were diagnosed following recurrent chest infections and pneumonia while others were diagnosed while being tested for something else. A majority of respondents were former smokers (62%).

To improve diagnosis and awareness of AATD, respondents rated: improving knowledge among General Practitioners; targeted screening programs in COPD/Asthma patients; and education for physicians as the most important areas.

The most challenging management aspects stated were decreased exercise tolerance; shortness of breath and not feeling fit or having the strength to do daily activities.

The most challenging treatment aspects were identified as: access issues to augmentation therapy; professional implications (i.e. loss of job) and access to classes to maintain fitness after rehabilitation. The most important areas to improve treatment were suggested as smoking cessation, developing other aspects of integral care and pulmonary rehabilitation.

All but two of the research areas were rated by 80% or more of respondents as ‘Important’ or ‘Very important’ with the top two most important identified as: research into the relationship between AATD and other diseases; and more evidence on the effectiveness of augmentation therapy.

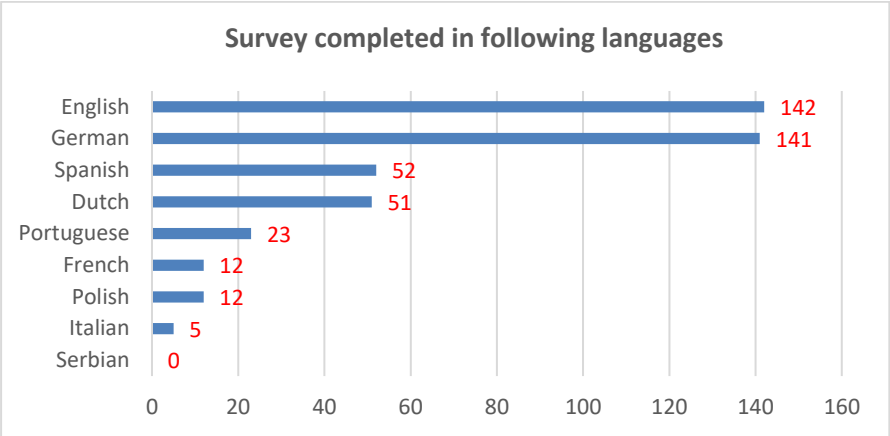
The most important areas to improve self-management and education were highlighted as: access to AATD specialised centres; access to reliable, easy-to-understand information about living with AATD and being able to recognise an exacerbation.

About the respondents

438 respondents out of a total of 440 were included for analysis as they met the criteria of being either a person with Alpha-1 antitrypsin deficiency (AATD) or a parent, relative or care-giver of someone with AATD. The 2 excluded respondents were medical professionals.

Respondent characteristics:

- 84% a person diagnosed with AATD and 16% a parent, relative or caregiver.
- 58% female, 41% male, 1% did not state.
- The mean age of respondents was 50 years.
- See chart below for number of survey respondents by survey language:

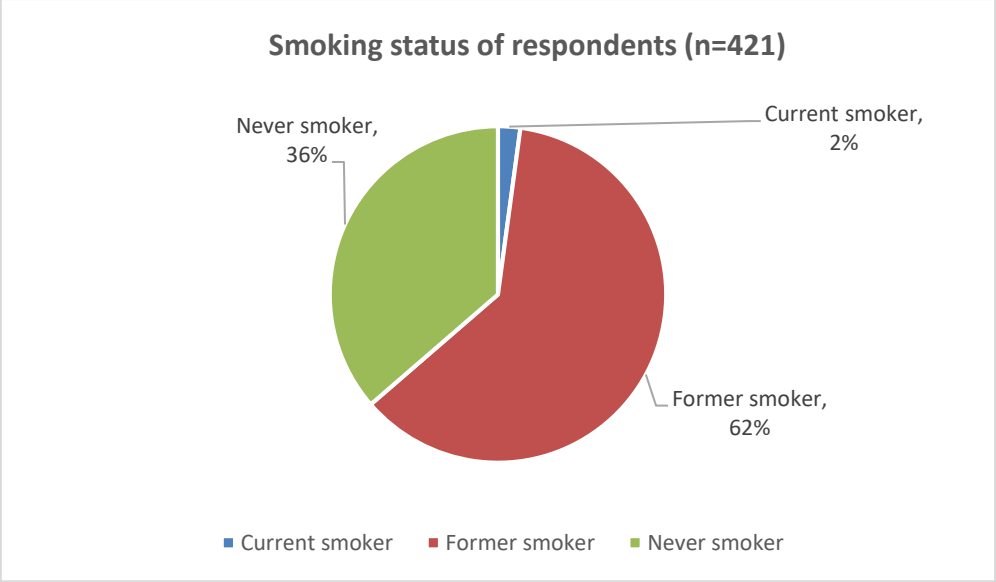


Respondents across all surveys were located in 26 countries/regions: Argentina, Australia, Austria, Belgium, Cyprus, Denmark, Ecuador, Finland, France, Germany, Ireland, Italy, Liechtenstein, Mexico, Netherlands, Norway, Poland, Portugal, Slovenia, Spain, South Africa, Sweden, Switzerland, United Kingdom, United States of America, Zimbabwe.

Additional characteristics

Smoking and alcohol use

- 55% of respondents drink alcohol.
- 62% of respondents were a former smoker, see chart below for full details:



Environmental exposure

Respondents (n=421) were asked if they were/are exposed to gases, fumes or dust in their professional activities and 71% said No (29% said Yes).

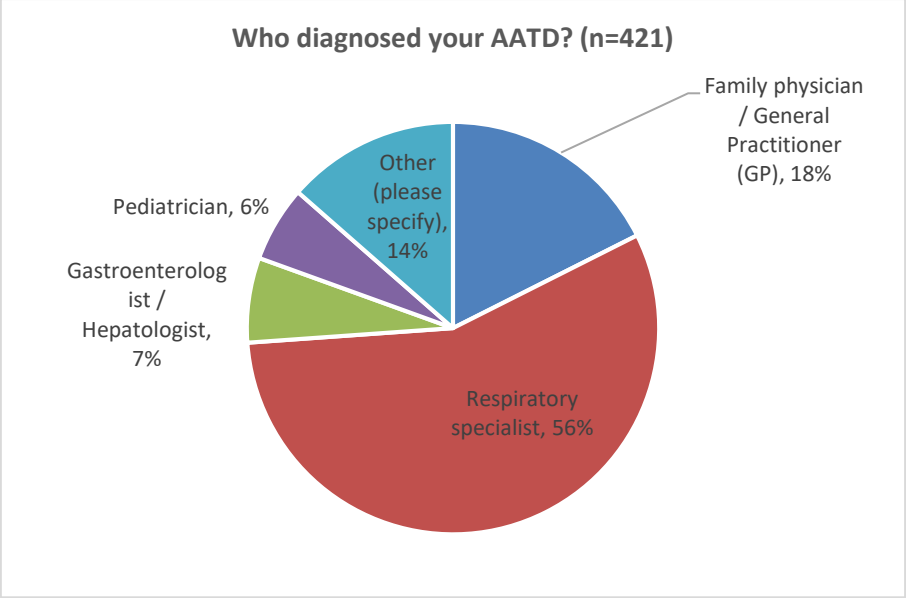
Transplants

Respondents were asked if they had had a lung and/or liver transplant:

- 4% of respondents have had a lung transplant (n=421)
- 1% of respondents have had a liver transplant (n=421)

Diagnosis

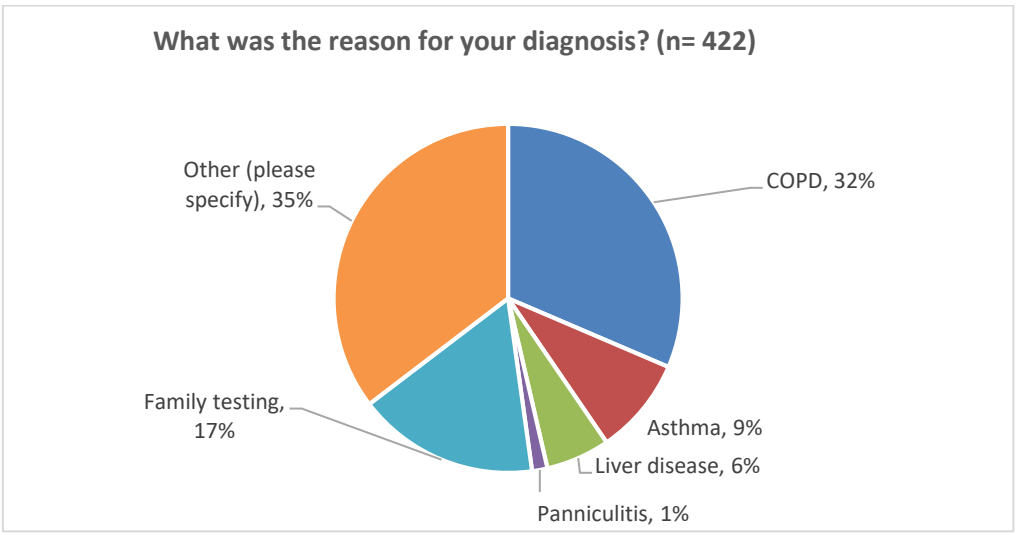
Who diagnosed?
Respondents were asked which healthcare professional diagnosed AATD with the majority stated a Respiratory specialist (56%) and Family doctor (18%). See chart on next page:



Answers in the 'Other' field included: Geneticist, Immunologist, Allergist, Dermatologist, Rheumatologist, Naturopath, Endocrine, Research laboratory, Hospital, Clinic, Myself.

Reason for diagnosis

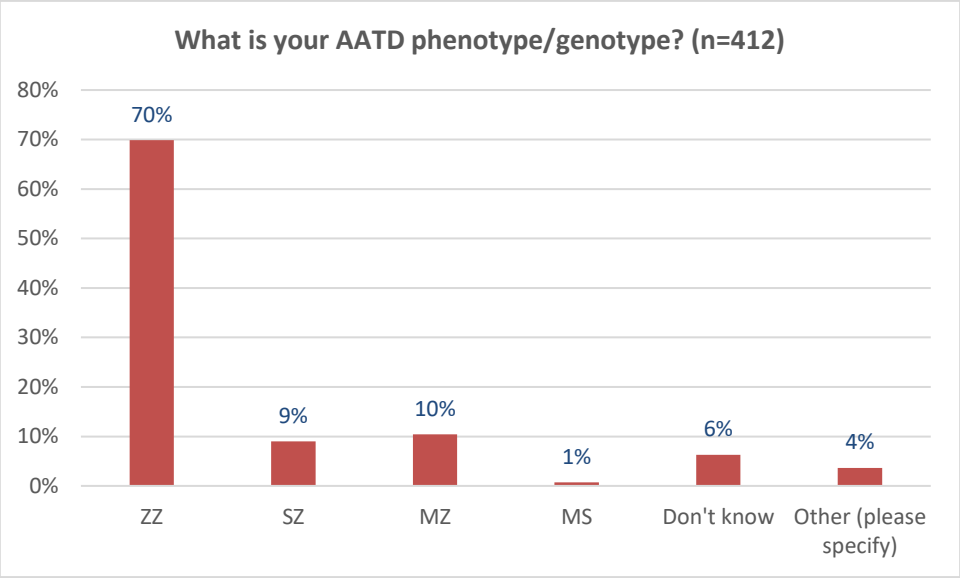
Respondents were also asked about the reason for their diagnosis and 32% stated COPD, 17% Family testing and 9% Asthma – see full results in chart below:



Other reasons given included: Breathing issues (n=14), Pneumonia (n=14), Chest infections (n=12), Liver issues (n=8), Accidental diagnosis (n=5), Weight loss (n=3), Emphysema (n=2), Swine flu (n=2), Cough (n=2) plus individuals who mentioned Fibromyalgia, Bronchiectasis, Bronchitis (n=3), Migraine, Tiredness, Low blood pressure, Inexplicable bleeds as a baby.

Phenotype

Respondents were asked about their AATD phenotype and 70% have ZZ phenotype; 10% MZ and 9% SZ. See chart below:



How long since diagnosis?

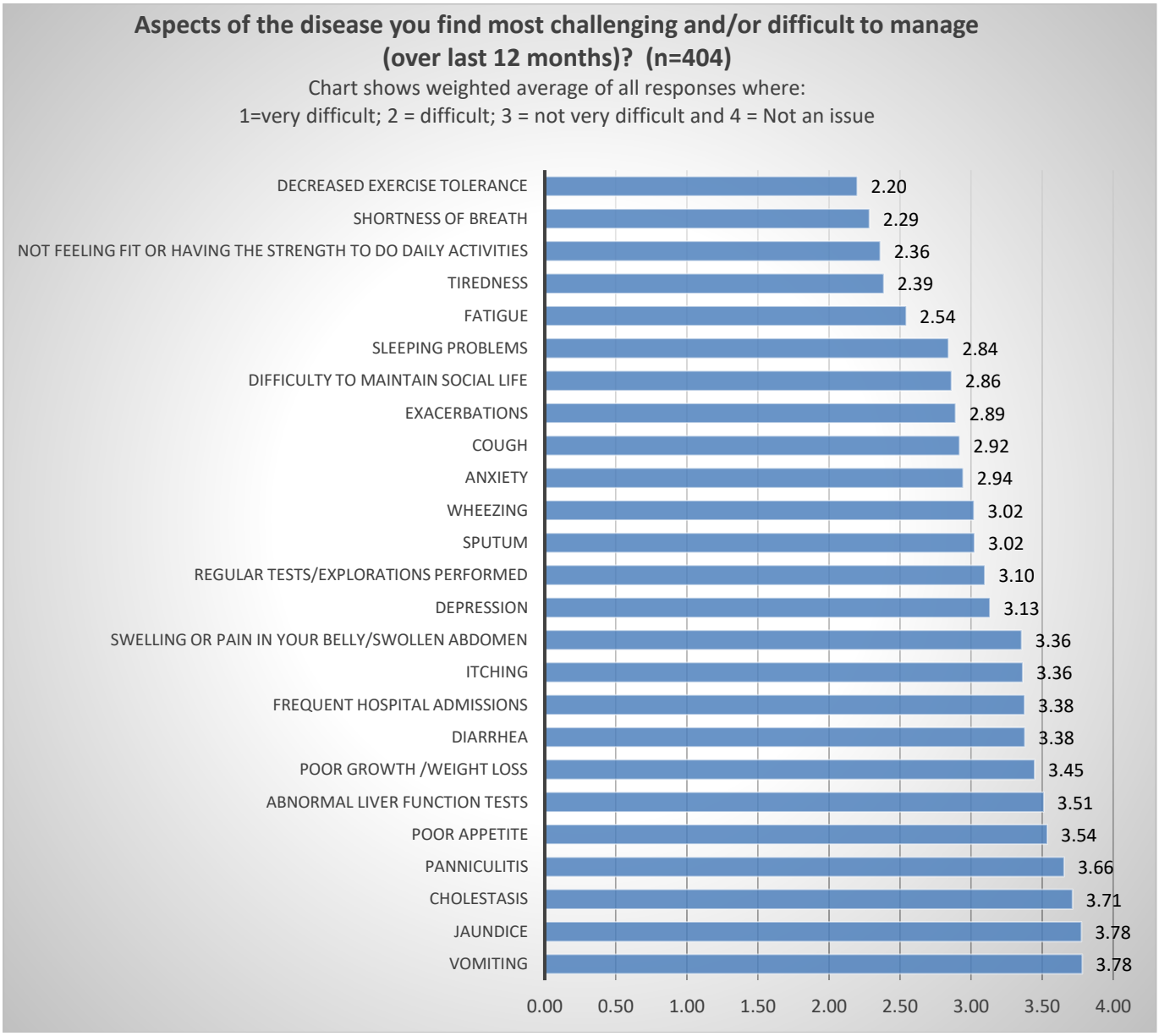
Respondents were asked how many years they had been diagnosed with AATD. The length ranged from 'less than 1 year' to 65 years with the average length since diagnosis being 12 years (median length was 9 years).

Your experience of AATD

Most challenging aspects to manage

Respondents were asked to rate which aspects of the disease they found most challenging and/or difficult to manage during the past 12 months. The Top 3 most challenging aspects:

1. Decreased exercise tolerance.
2. Shortness of breath.
3. Not feeling fit or having the strength to do daily activities.



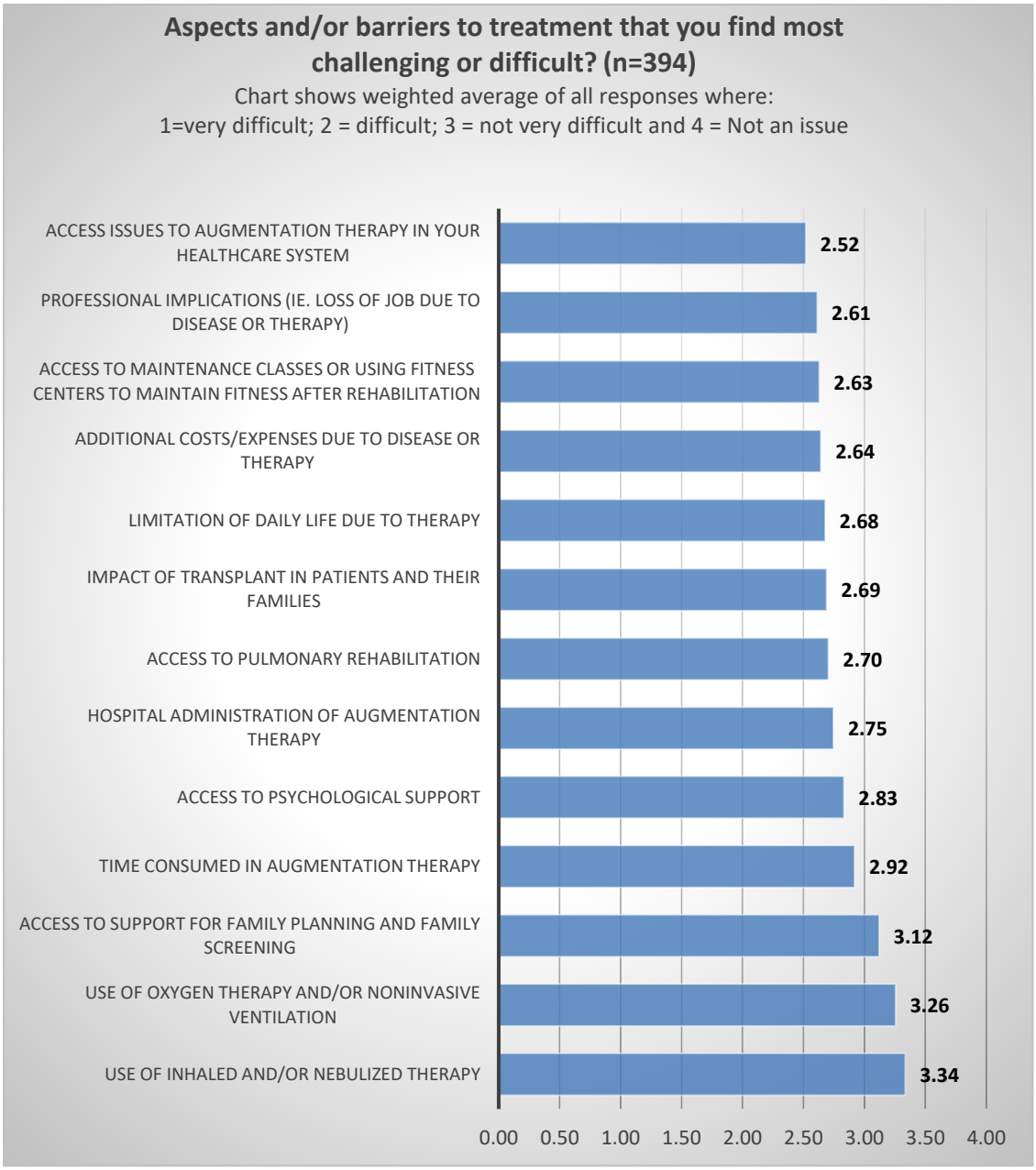
"Overwhelming difficulty in losing all aspects of normal life. No motivation as no hope of recovery" (Respondent, EN survey).

"The fact that protein replacement therapy is being applied to my home by specialised laboratory personnel seems very important to my quality of life. That allows me to continue with my work and rehabilitation activities." (Respondent, ES survey (translated).

Most challenging aspects/barriers for treatment

Respondents were asked to rate which aspects and/or barriers for treatment do you find most challenging and difficult to manage. The Top 3 most challenging aspects were:

1. Access issues to augmentation therapy in your healthcare system.
2. Professional implications (i.e., loss of job due to disease or therapy).
3. Access to maintenance classes or using fitness centres to maintain fitness after rehabilitation



"I struggle with oxygen therapy as I have anxiety when I wear it as people stare and comment. This makes me reclusive." (Respondent, EN survey).

"Too many visits in hospitals" (Respondent, FR survey, translated)

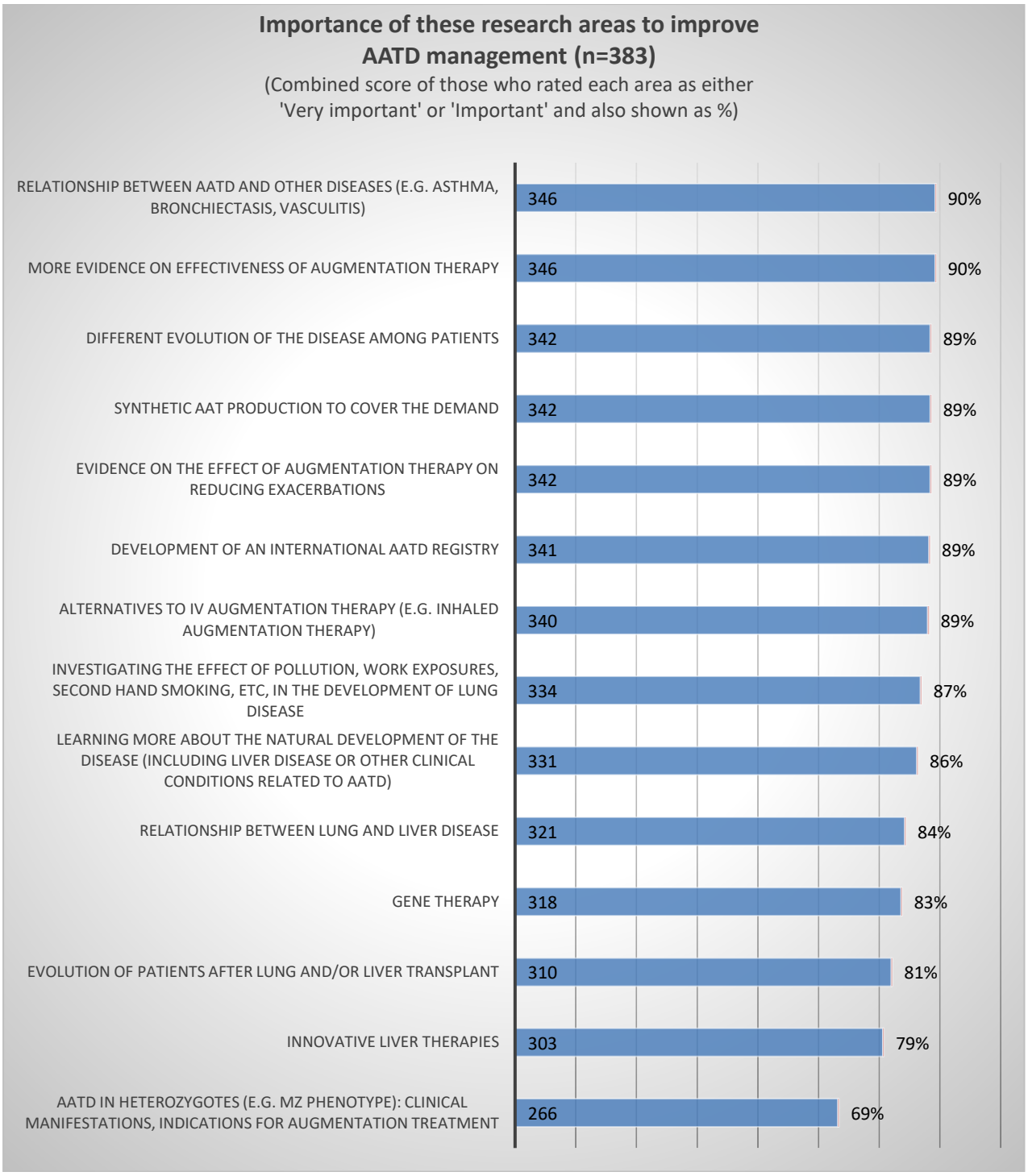
"The fact that protein replacement therapy is being applied to my home by specialised laboratory personnel seems very important to my quality of life. That allows me to continue with my work and rehabilitation activities." (Respondent, ES survey (translated).

Research prioritisation

Improving AATD management

Respondents were asked to rate how important a list of research areas were to improve AATD management. The top most important research areas being:

1. Relationship between AATD and other diseases (90%)
2. More evidence on effectiveness of augmentation therapy (90%)
3. 5 areas of research came in at 89% - see chart below for full details:

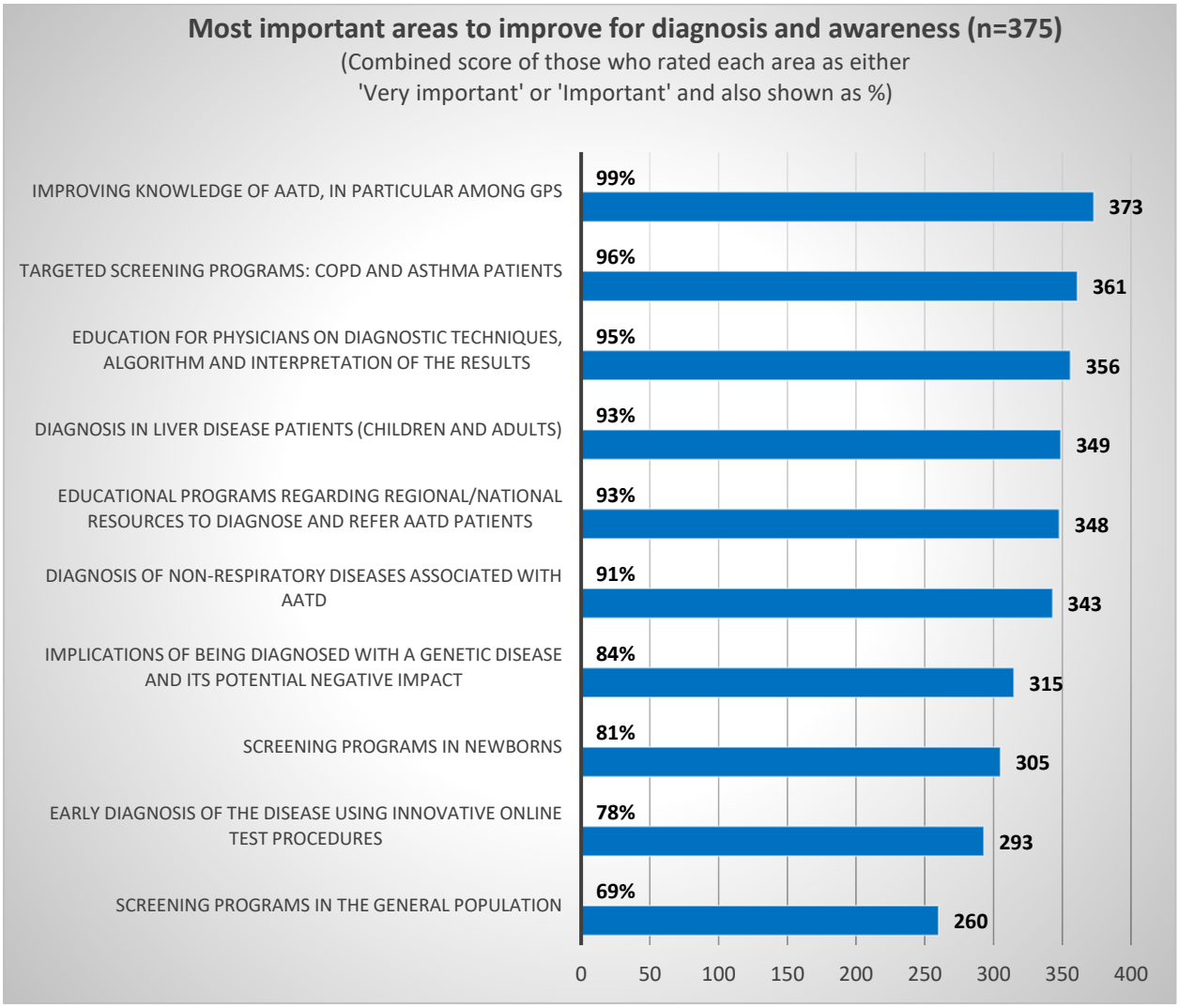


"The development of a drug or a method to stop lung deterioration or to cure pulmonary emphysema" (Respondent, DE survey, translated)
"Examination of why children with MZ are more likely to have asthma, bronchitis or pneumonia" (Respondent, DE survey, translation)
"Very important to start investigating heterozygotes that have very low blood AAT values and to consider them as risk patients" (Respondent, PT survey, translation)
"Diagnosing AAT in early childhood to avoid risk factors" (Respondent, PL survey, translation)
"In particular, investigate the reasons why one patient leads a reasonable life and another is continuously ill" (Respondent, NL survey, translation)

Improving diagnosis and awareness of AATD

Respondents were asked to rate a list of areas as to how important each is to improve diagnosis and awareness of AATD. All but 2 areas were rated as 80% or higher with the top 3 most important being:

1. Improving knowledge of AATD, in particular among General Practitioners (99%)
2. Targeted screening programs: COPD and Asthma patients (96%)
3. Education for physicians on diagnostic techniques, algorithm, interpretation of results (95%)



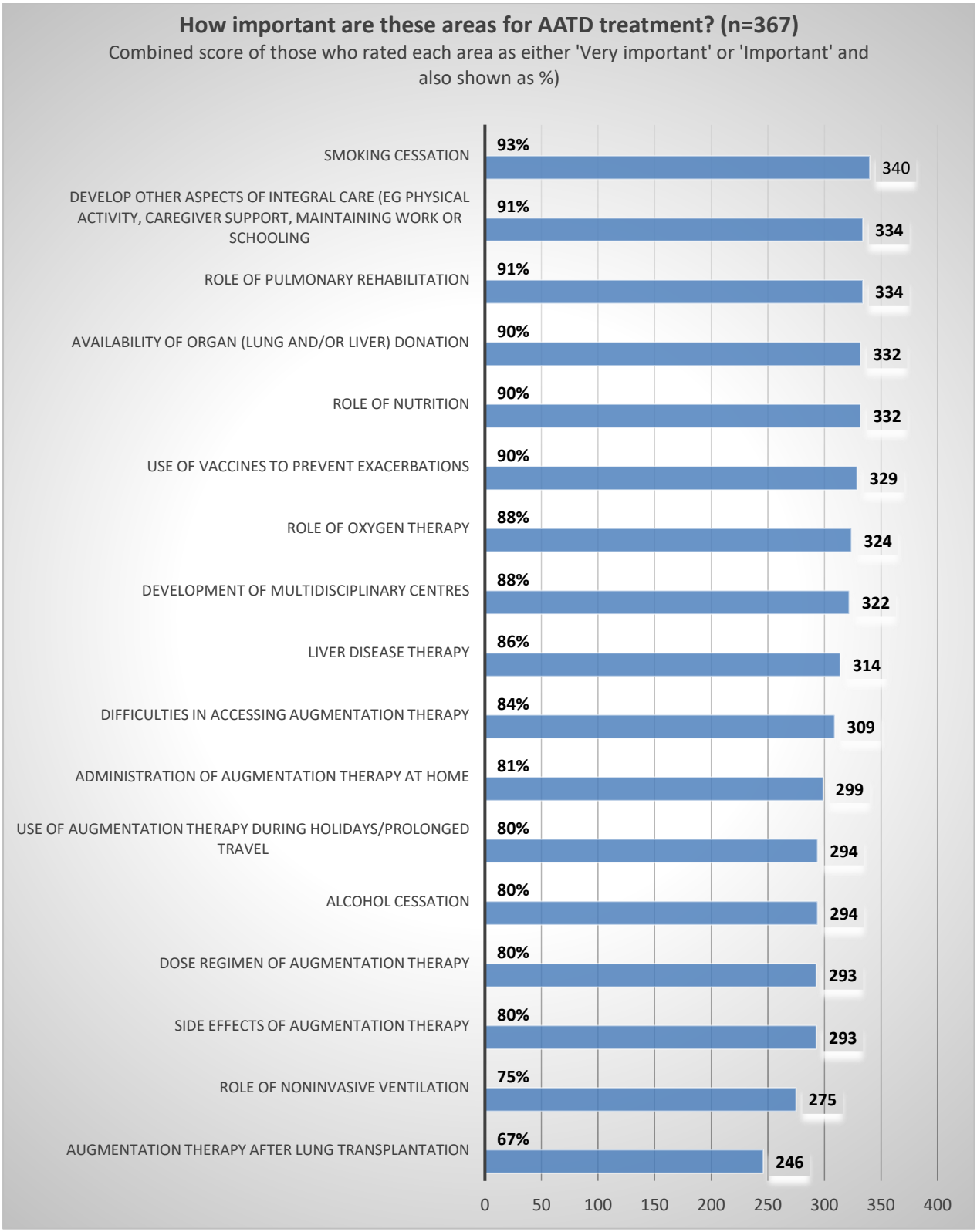
"It is very important that general practitioners are educated because most of them know nothing about it" (Respondent, EN survey)

"Family members should be tested if a case of AATD has been detected" (Respondent, DE survey, translation)

Improving treatment

Respondents were asked to rate a list of areas as to how important each is to improve treatment of AATD. The results in the chart below show the combined scores of those who rated an area as 'Very important' and 'Important'. The top 3 were:

1. Smoking cessation (93%)
2. Develop other aspects of integral care (e.g. physical activity, care-giver support, maintaining work or schooling, nutrition, psychological care, sex-life, daily life) - 91%
3. Role of Pulmonary rehabilitation (91%)

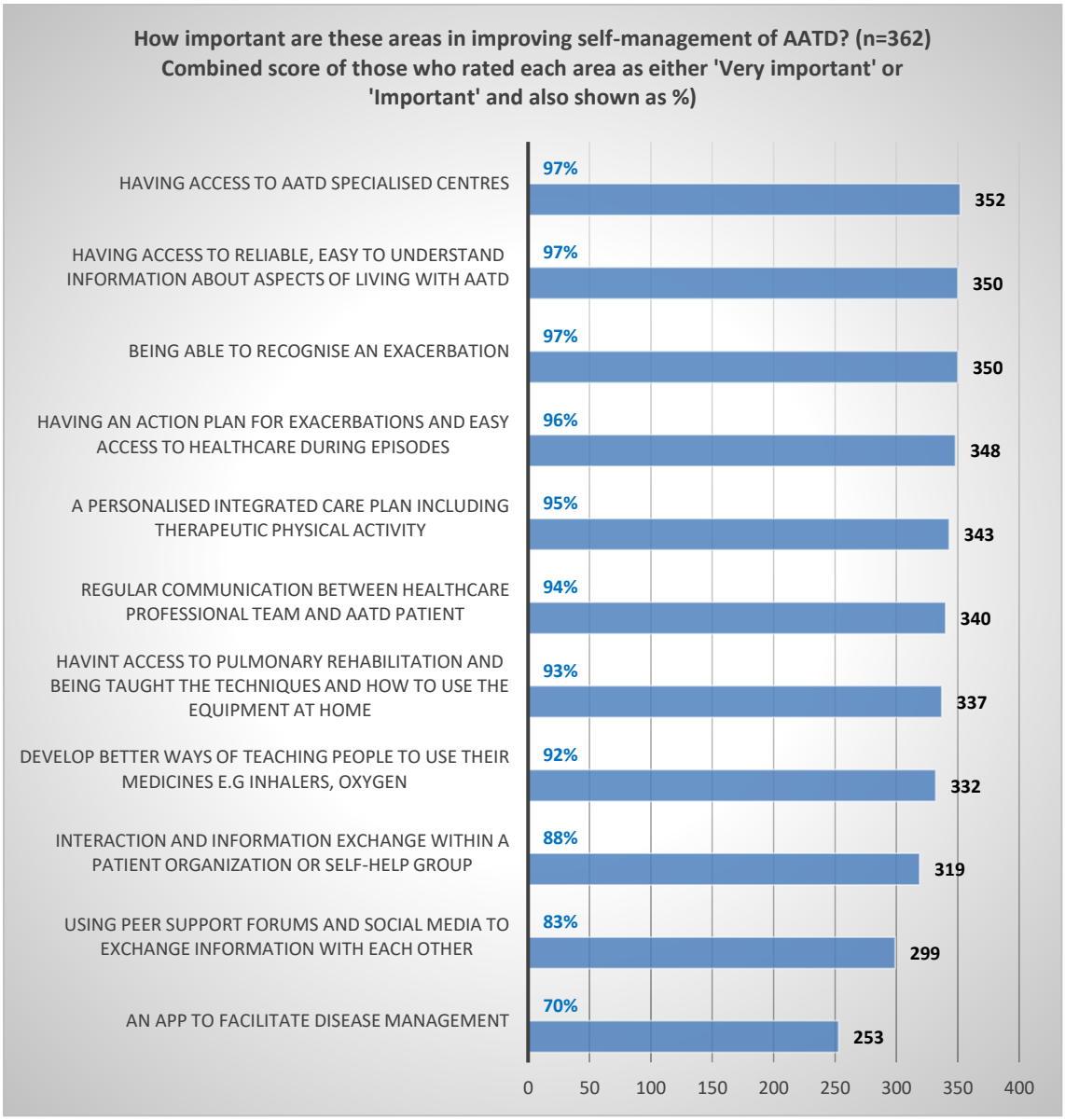


"Being very susceptible to bacteria and viruses is therefore often lonely. Because, especially in the winter months, you are careful not to get sick among people." (Respondent, NL Survey, translated)

Self-management and education

Respondents were asked to rate a list of areas as to how important each is to improve self-management of AATD. The top 3 most important being:

1. Access to AATD specialised centres (97%)
2. Access to reliable, easy to understand information about living with AATD (97%)
3. Being able to recognise an exacerbation (97%)



"I have experienced very long wait times for pulmonary rehabilitation. Approximately 6 months for a 6-week course with no follow up. I found this to be typical through contact from social media" (Respondent, EN survey)

"Peer support meetings are very useful you can learn from each other. But keep it in the spring e.g. In May, June. Many of these are meetings in Sept, Oct. Then there is usually flu and then many people do not participate in order not to get sick." (Respondent, NL survey, translated)

General comments from survey respondents

"Research is important but early diagnosis among new-borns is the most important thing that needs to be done" (Respondent, EN survey).

"DCLO (Diffusing capacity of the lungs for carbon monoxide) not given the attention it deserves regarding treatment guidelines i.e. alphas with good FEV1 but bad DLCO can miss out on augmentation therapy and die prematurely" (Respondent, EN survey).

"Remote monitoring via iPhone as is now done in the US for chronic conditions would be useful, including to avoid breathing anxiety fits, unnecessary hospitalisations etc." (Respondent, EN survey).

"The change of climate, and the cold make breathing difficult, living more than 2000 metres above sea level makes breathing difficult" (Respondent, ES survey, translation).

"Access to lung sports group in my region an impossibility (eternal waiting) or very miserable quality" (Respondent, DE survey, translation).

"No reference centre where we are with doctors of various specialities" (Respondent, PT survey, translation).

"Help patients without treatment. In countries that do not know about Alpha 1, we remain weakened and without hope of having the protein." (Respondent, ES survey, translation).

"When waiting for a lung transplant, have more information regarding the progession in the list with passing time. Very scary to stay without news. Confusion between list position and donor compatibility (lung size, blood type etc)" (Respondent, FR survey, translation).

"A case manager who can co-ordinate and organise things" (Respondent, NL survey, translation)

Appendices

Appendix 1: Data from the German language survey

A total of **141 respondents** to the German-language survey:

Characteristics:

- 87% (n=123) a person diagnosed with AATD and 13% (n=18) a parent, relative or caregiver.
- 57% female, 43% male.
- The mean age of respondents was 51 years.
- Respondents who completed the survey were located in the following countries: Germany (n=113), Switzerland (n=16), Austria (n=6), Denmark (n=1), France (n=-1), Liechtenstein (n=1), Netherlands (n=1), Norway (n=1), Sweden (n=1).

Smoking and alcohol:

- 58% of respondents drink alcohol.
- 60% of respondents were a former smoker; 39% never-smoker and 1% current smoker.

Environmental exposure

Respondents (n=136) were asked if they were/are exposed to gases, fumes or dust in their professional activities and 70% said No (30% said Yes).

Transplants

Respondents (n=136) were asked if they had had a lung and/or liver transplant:

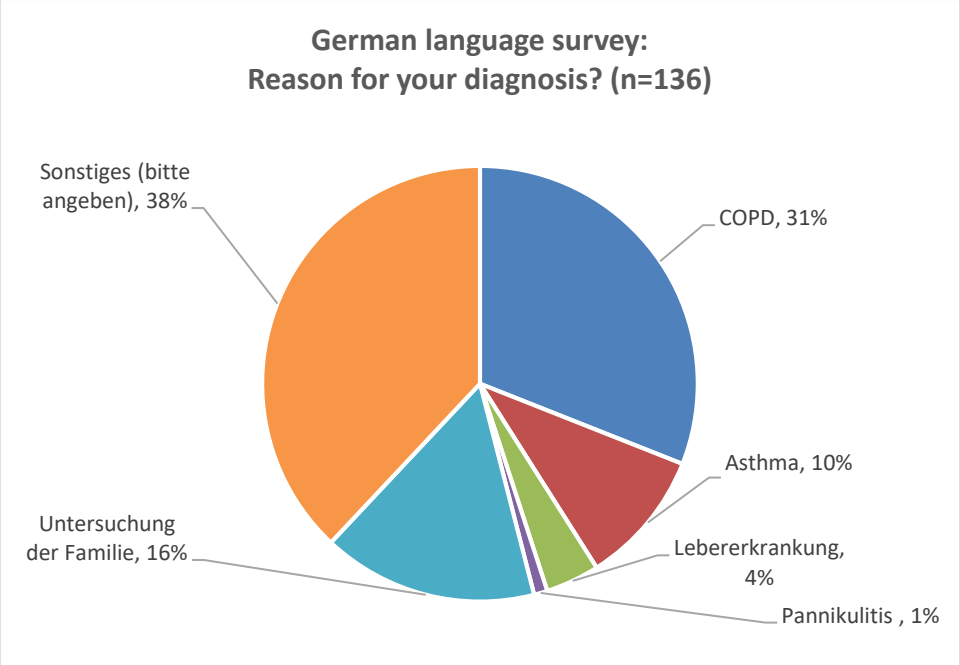
- 4% of respondents have had a lung transplant (n=6)
- 1% of respondents have had a liver transplant (n=1)

Diagnosis

Respondents (n=136) were asked which healthcare professional diagnosed AATD:

- Respiratory specialist (e.g. pulmonologist) (60%)
- Family doctor (15%)
- Gastroenterologist/hepatologist (5%)
- Paediatrician (5%)
- Other (15%) – including Rehabilitation Doctor; Hospital; Molecular Biology Institute; Research Company; Geneticist; Naturopath.

Respondents (n=136) were also asked about the reason for their diagnosis and 31% stated COPD, 17% Family testing and 10% Asthma – see full results in chart:



Other reasons given included: Infections/pneumonia (n=9); shortness of breath (n=10); heavy weight loss (n=2); cough (n=1); bronchiectasis (n=1); bronchitis (n=3); diagnosis of a family member (n=5); inefficiency (n=1); allergies (n=1); body weakness (n=2); slight nosebleeds in infants 9n=1); vitamin K deficiency (n=1); unclear digestive problems (n=1).

AATD phenotype: 75% have ZZ phenotype; 14% MZ; 6% SZ and 1% MS; 1% did not know and the rest did not state.

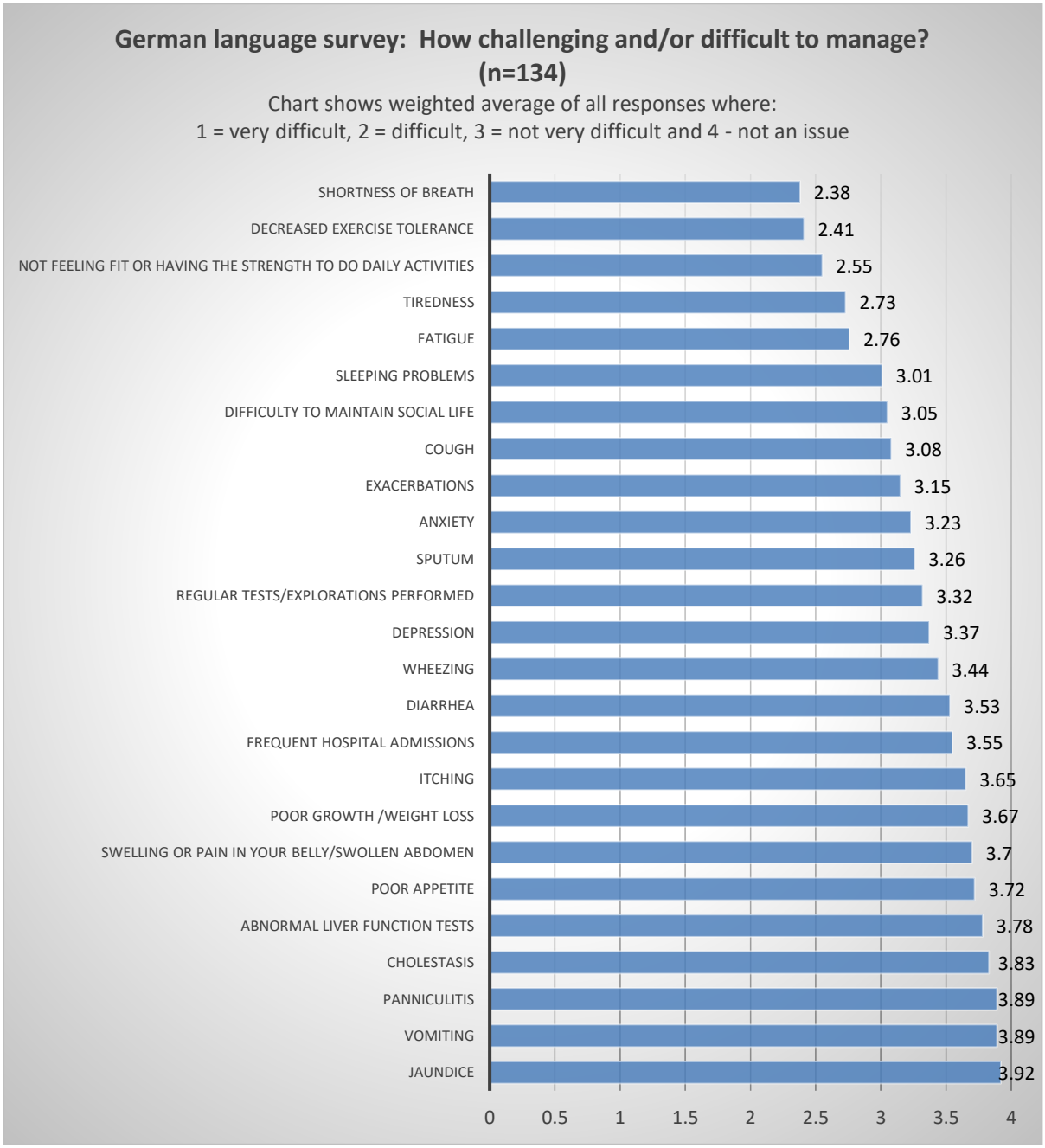
How many years had they been diagnosed with AATD: this ranged from '1 year' to 59 years with the mean length since diagnosis being 12 years.

Your experience of AATD

Most challenging aspects of AATD

Respondents were asked to rate which aspects of the disease they found most challenging and/or difficult to manage during the past 12 months. The Top 3 most challenging aspects were:

1. Shortness of breath.
2. Decreased exercise tolerance.
3. Not feeling fit or having the strength to do daily activities.



"Angioödeme" – Angioedema

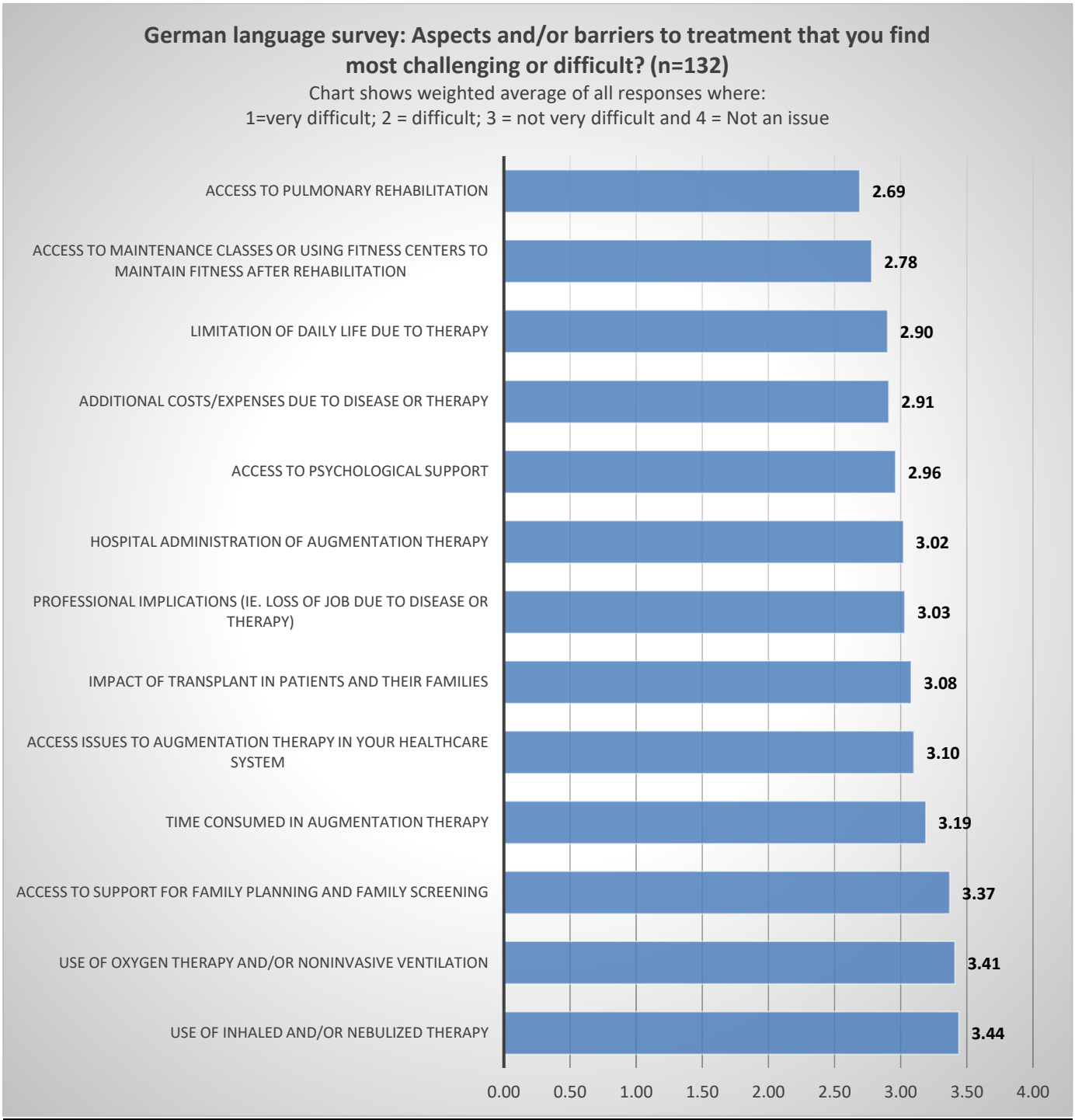
"Verstärkte Warzenbildung" – Increased wart formation

"Schmerzen im Brustkorb" - Chest pain

Most challenging aspects/barriers for treatment

Respondents were asked to rate which aspects and/or barriers for treatment do you find most challenging and difficult to manage. The Top 3 most challenging aspects were:

1. Access to pulmonary rehabilitation.
2. Access to maintenance classes or using fitness centres to maintain fitness after rehabilitation
3. Limitation of daily life due to therapy.

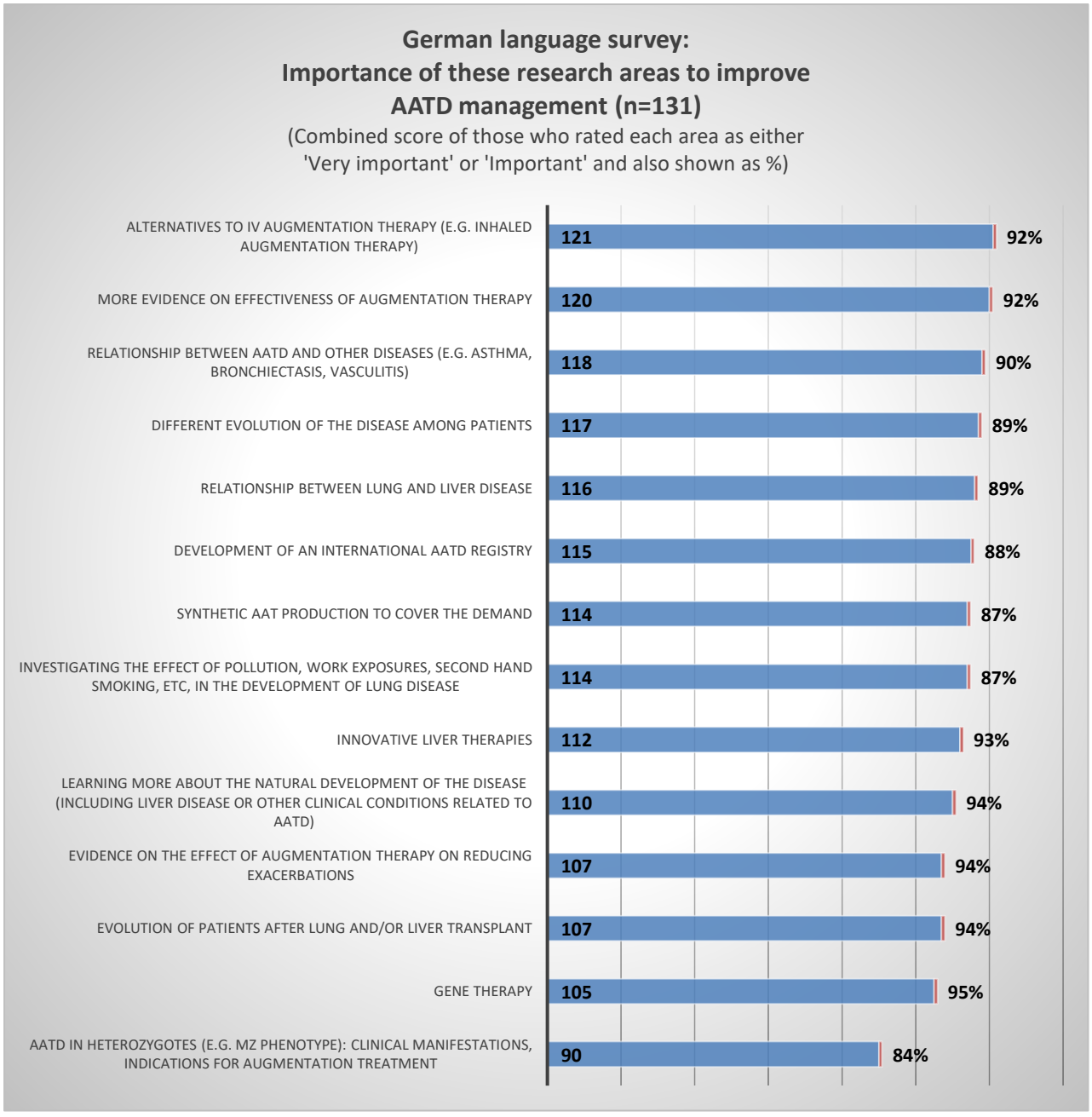


Areas of Research

Improving AATD management

Respondents were asked to rate how important a list of research areas was to improve AATD management. The results below show the combined scores of those who rated an area as 'Very important' and 'Important'. The top most important research areas being:

1. Alternatives to IV Augmentation Therapy (92%)
2. More evidence on effectiveness of augmentation therapy (92%)
3. Relationship between AATD and other diseases (90%)

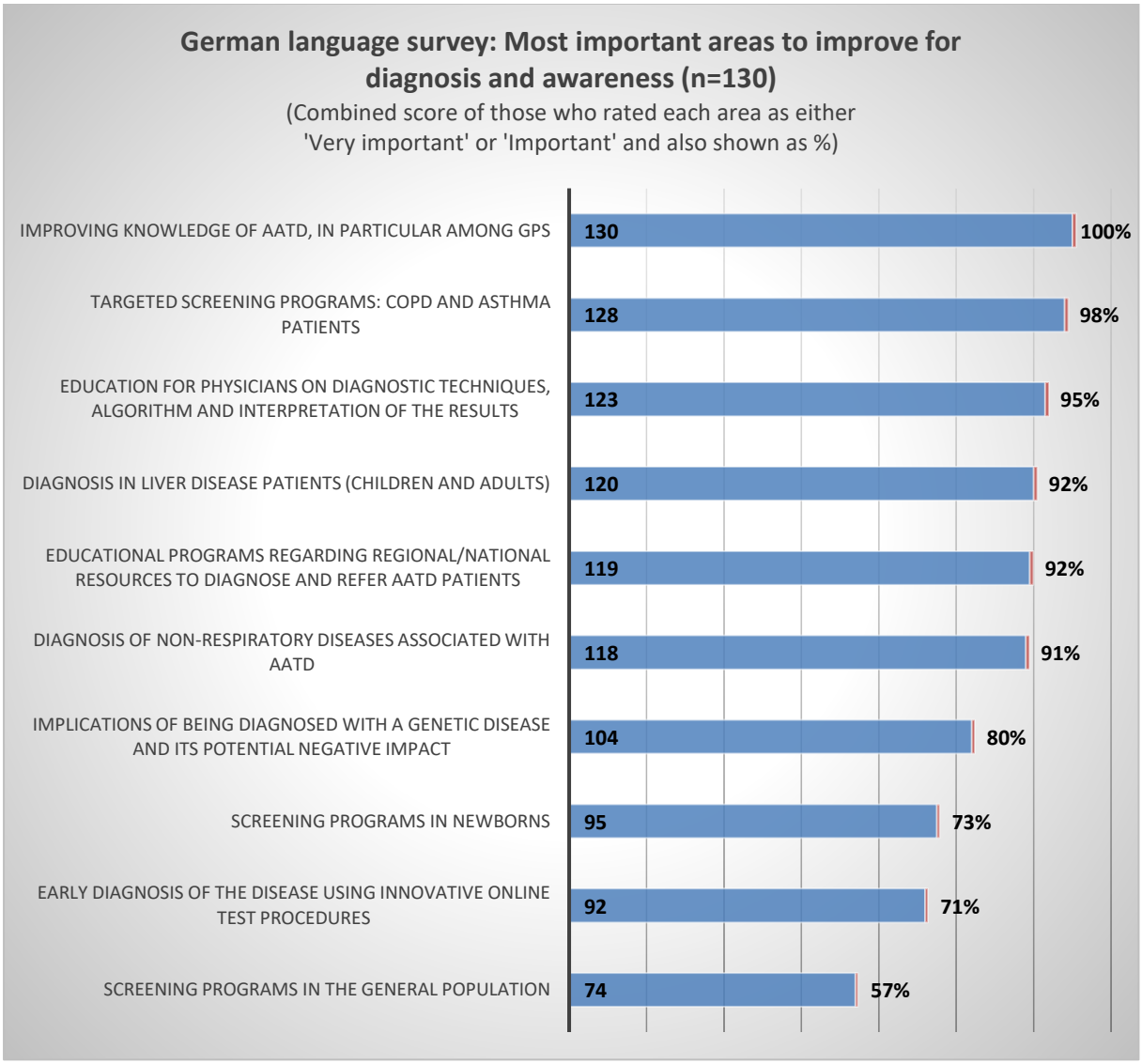


"Mehr Austausch unter Aphas" – More exchange among alphas

Improving diagnosis and awareness of AATD

Respondents were asked to rate a list of areas as to how important each is to improve diagnosis and awareness of AATD. The top 3 rated as most important being:

1. Improving knowledge of AATD, in particular among General Practitioners (100%)
2. Targeted screening programs: COPD and Asthma patients (98%)
3. Education for physicians on diagnostic techniques, algorithm, interpretation of results (95%)



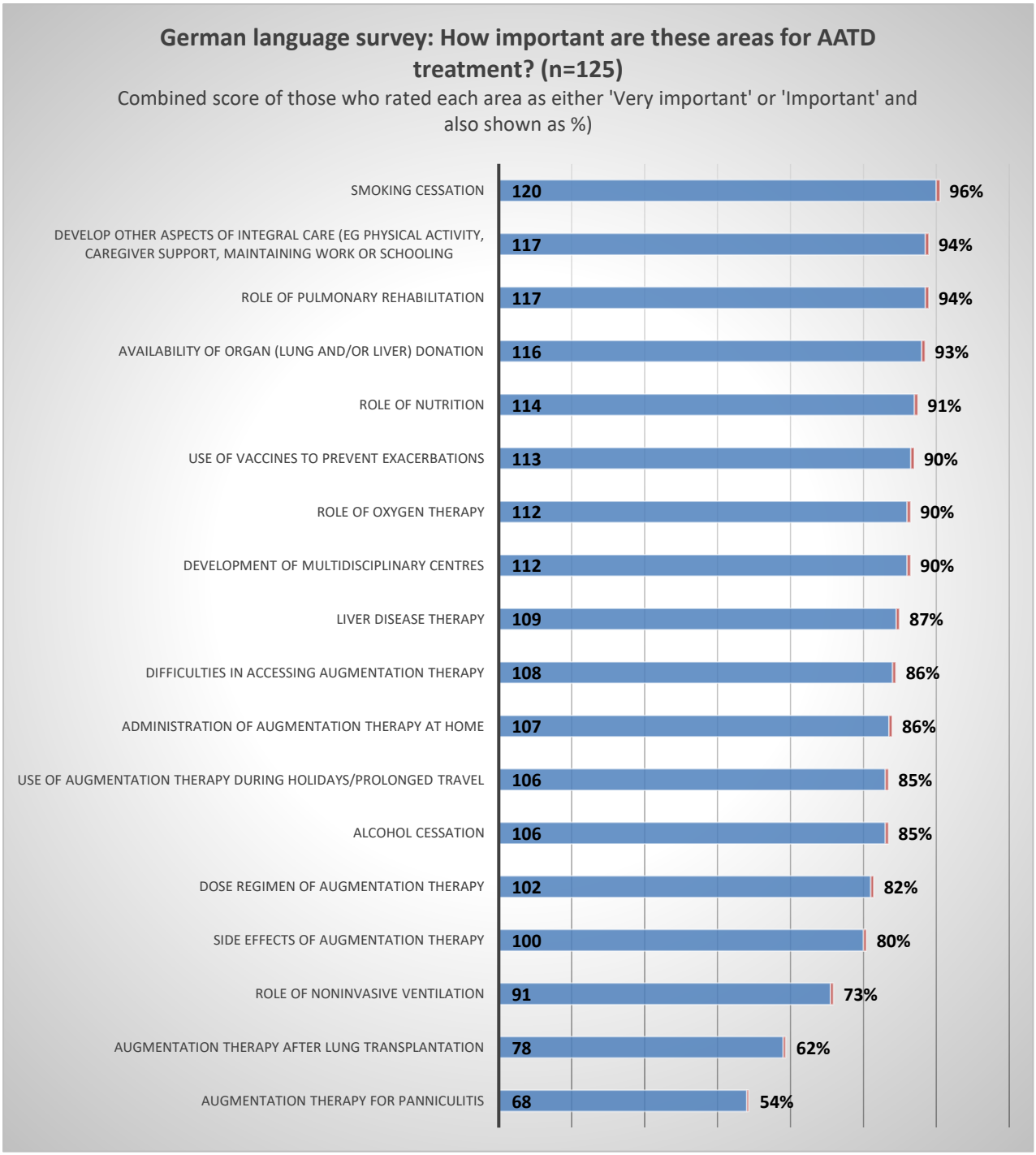
"Allgemeine Informationen zur Krankheit. Musste meiner Behindertstelle aufklären um was es sich für eine Krankheit es ist" - General information about the disease.

Das jeder Lungenarzt bei Patienten mit Emphysem einen Alphatest automatisch macht" - Every pulmonologist in patients with emphysema automatically does an alpha test

Improving treatment

Respondents were asked to rate a list of areas as to how important each is to improve treatment of AATD. The results in the chart below show the combined scores of those who rated an area as 'Very important' and 'Important'. The top 3 rated areas were:

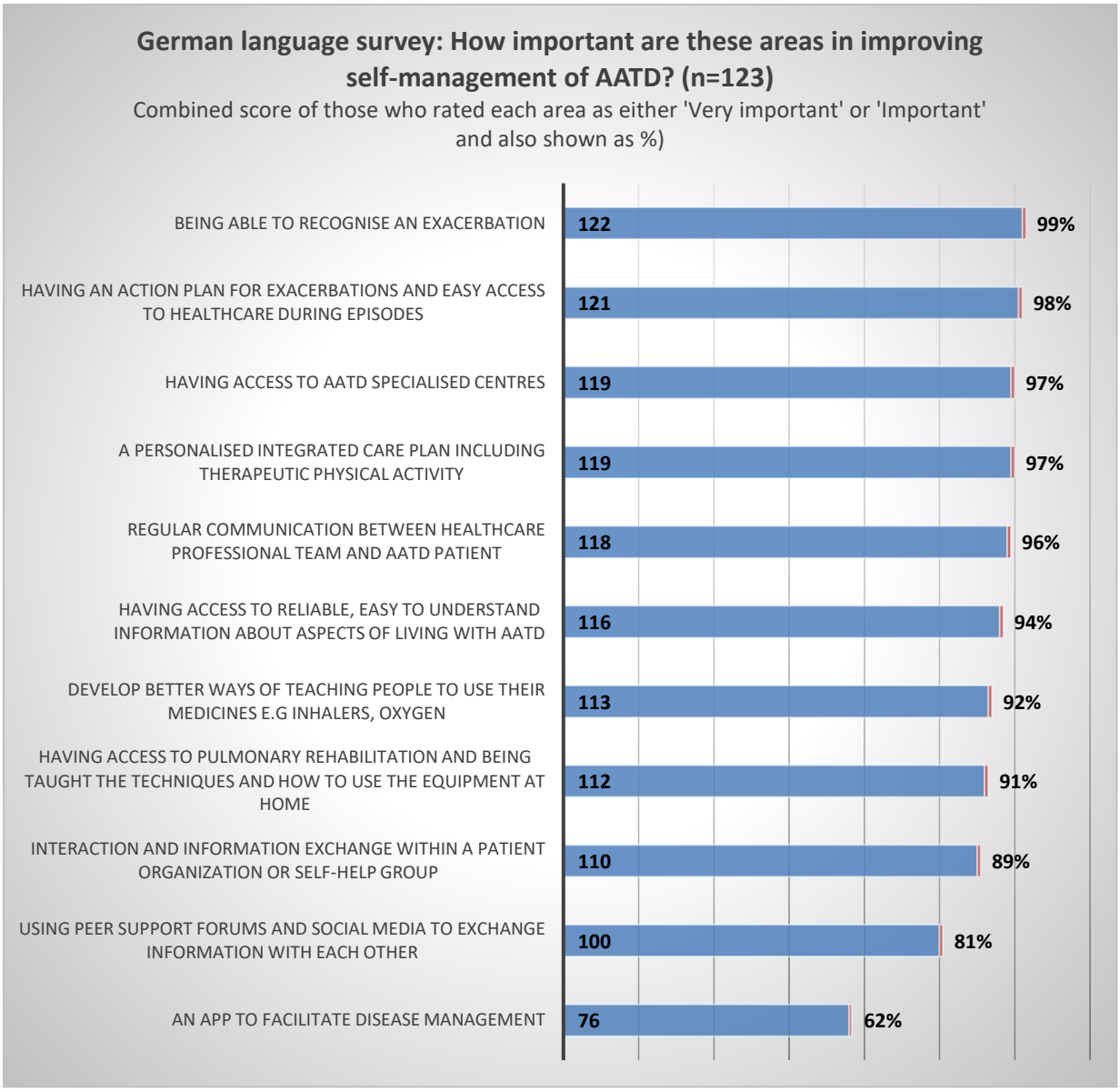
1. Smoking cessation (96%)
2. Develop other aspects of integral care (e.g. physical activity, care-giver support, maintaining work or schooling, nutrition, psychological care, sex-life, daily life) - 94%
3. Role of Pulmonary rehabilitation (94%)



Self-management and education

Respondents were asked to rate a list of areas as to how important each is to improve self-management of AATD. The top 3 most important being:

1. Being able to recognise an exacerbation (99%)
2. Having an action plan for exacerbations and easy access to healthcare during episodes (98%)
3. Access to AATD specialised centres (97%) and A personalised integrated care plan (97%)



"Mehr Lungensportgruppen es gibt viel zu wenige" – More Pulmonary Sports there are far too few

Appendix 2: Data from the English language survey only

A total of **142 respondents** to the English-language survey:

Characteristics:

- 88% (n=125) a person diagnosed with AATD and 12% (n=17) a parent, relative or caregiver.
- 65% female, 34% male, 1% prefer not to say.
- The mean age of respondents was 52 years.
- Respondents who completed the survey were located in the following countries: United Kingdom (n=94), USA (n=12), Sweden (n=10), Denmark (n=7), Norway (n=6), Ireland (n=4), Germany (n=2), Finland (n=2), Australia (n=1), Slovenia (n=1), Cyprus (n=1), Canada (n=1), Belgium (n=1)

Smoking and alcohol:

- 58% of respondents drink alcohol.
- 63% of respondents were a former smoker; 33% never-smoker and 4% current smoker.

Environmental exposure
Respondents (n=136) were asked if they were/are exposed to gases, fumes or dust in their professional activities and 68% said No (32% said Yes).

Transplants
Respondents (n=136) were asked if they had had a lung and/or liver transplant:

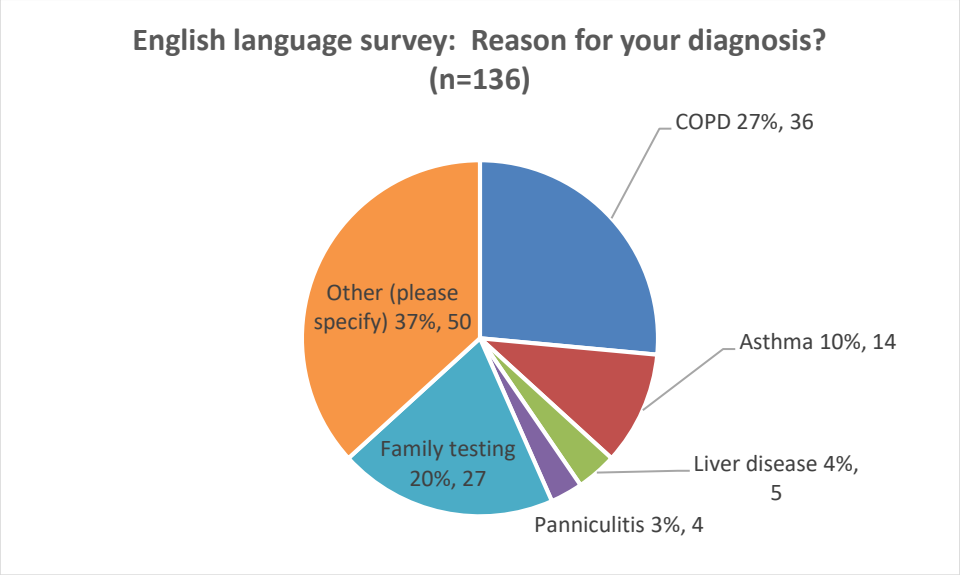
- 2% of respondents have had a lung transplant (n=3)
- 1% of respondents have had a liver transplant (n=1)

Diagnosis

Respondents (n=136) were asked which healthcare professional diagnosed AATD:

- Respiratory specialist (e.g. pulmonologist) (44%)
- Family doctor (32%)
- Gastroenterologist/hepatologist (7%)
- Paediatrician (4%)
- Other (13%) – including Hospital; Geneticist; Dermatologist; Immunologist; Rheumatologist.

Respondents (n=136) were also asked about the reason for their diagnosis and 26% stated COPD, 20% Family testing and 10% Asthma – see full results in chart on next page:



Other reasons given included: Infections/pneumonia (often recurring) (n=14); when looking for/treating something else (n=6); shortness of breath (n=5); diagnosis of a family member (n=3); tiredness(n=3); weight loss (n=2); bronchiectasis (n=2); bronchitis (n=2); swine flu (n=2); aspergillosis (n=1); emphysema (n=1); abnormal liver function test (n=1); baby colic (n=1); jaundice (n=2); cough (n=1); ulcerative colitis (n=1).

AATD phenotype: 63% have ZZ phenotype; 7% MZ; 13% SZ and 1% MS; 11% did not know and 4% described as: Pi Z (n=1); Z null (n=2); Snull (n=1) and Ss (n=1).

How many years had they been diagnosed with AATD: this ranged from 'less than 1 year' to 45 years with the mean length since diagnosis being 11 years.

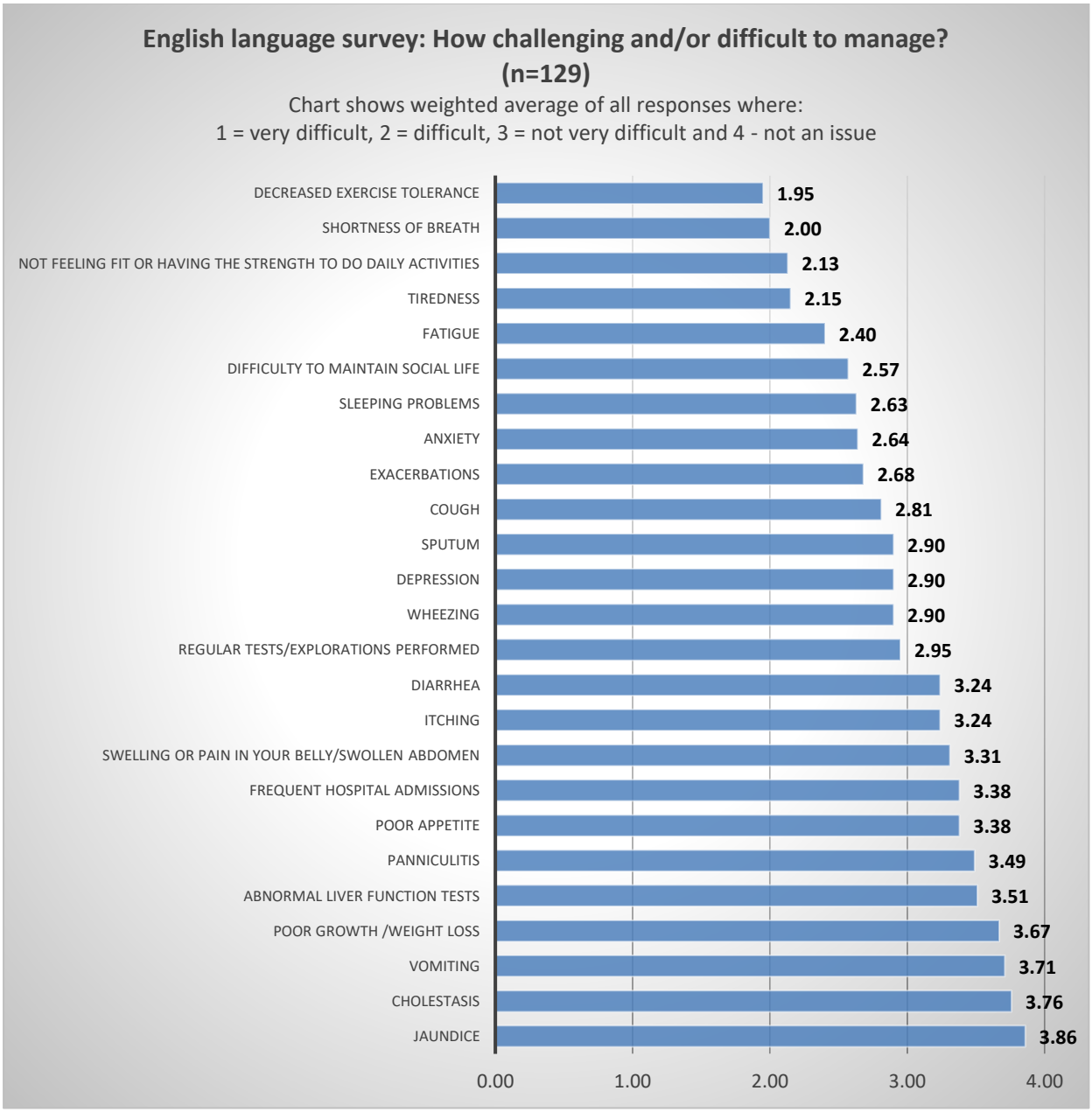
Your experience of AATD

Most challenging aspects of AATD

Respondents were asked to rate which aspects of the disease they found most challenging and/or difficult to manage during the past 12 months.

The Top 3 most challenging aspects were:

1. Decreased exercise tolerance.
2. Shortness of breath.
3. Not feeling fit or having the strength to do daily activities.

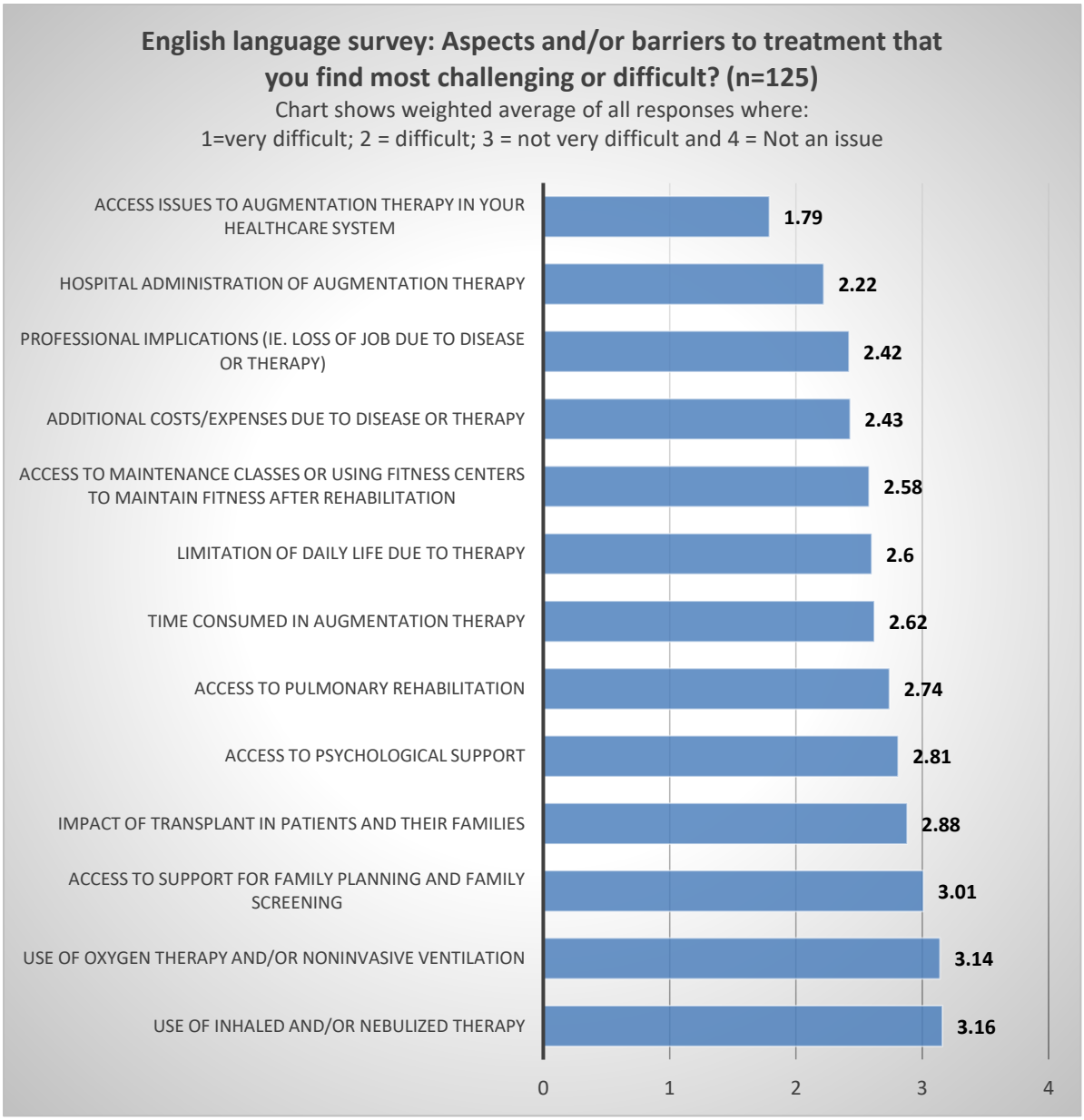


"Overwhelming difficulty in losing all aspects of normal life. No motivation as no hope of recovery."
"Intolerance to poor air quality (I live in London)"

Most challenging aspects/barriers for treatment

Respondents were asked to rate which aspects and/or barriers for treatment do you find most challenging and difficult to manage. The Top 3 most challenging aspects were:

1. Access issues to augmentation therapy in your healthcare system.
2. Hospital administration of augmentation therapy.
3. Professional implications (i.e. loss of job).



"Knowledge and treatment of alpha-1 antitrypsin deficiency in Sweden is almost non-existence for us patients."

"We don't get augmentation therapy in the UK that's the whole point. There is something that can't prolong a symptomatic sufferer's life, but we are not allowed it. Disgusting also being mZ even the specialists deny you any support uttered devastated my world as u have a young child."

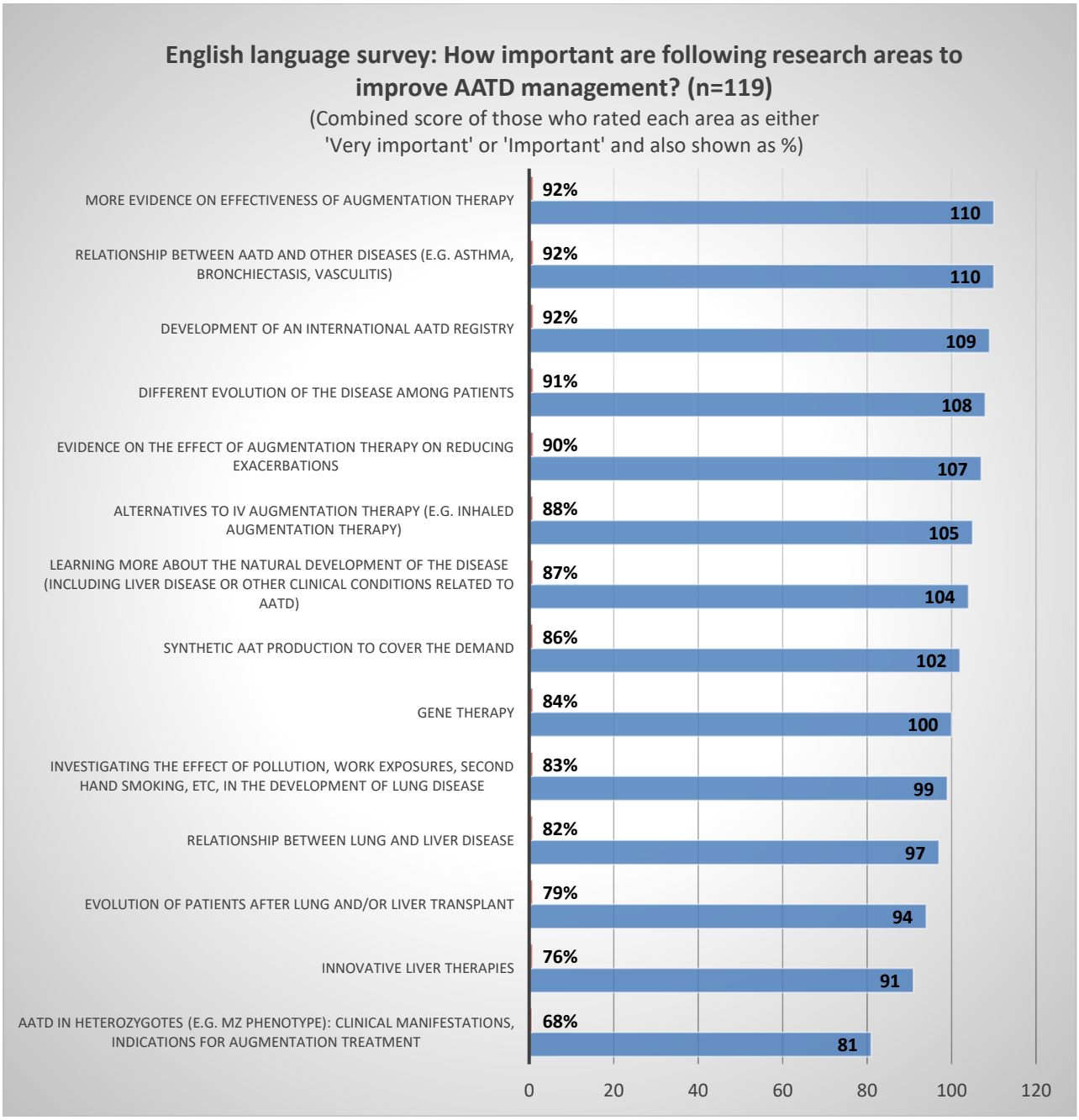
"It is time consuming to make sure I do enough exercise to keep my lungs healthy, and expensive to eat well. Also expensive to pay for gym membership"

Areas of Research

Improving AATD management

Respondents were asked to rate how important a list of research areas was to improve AATD management. The results below show the combined scores of those who rated an area as 'Very important' and 'Important'. The top most important research areas being:

1. More evidence on effectiveness of augmentation therapy (92%)
2. Relationship between AATD and other diseases (92%)
3. Development of an international AATD registry (92%)



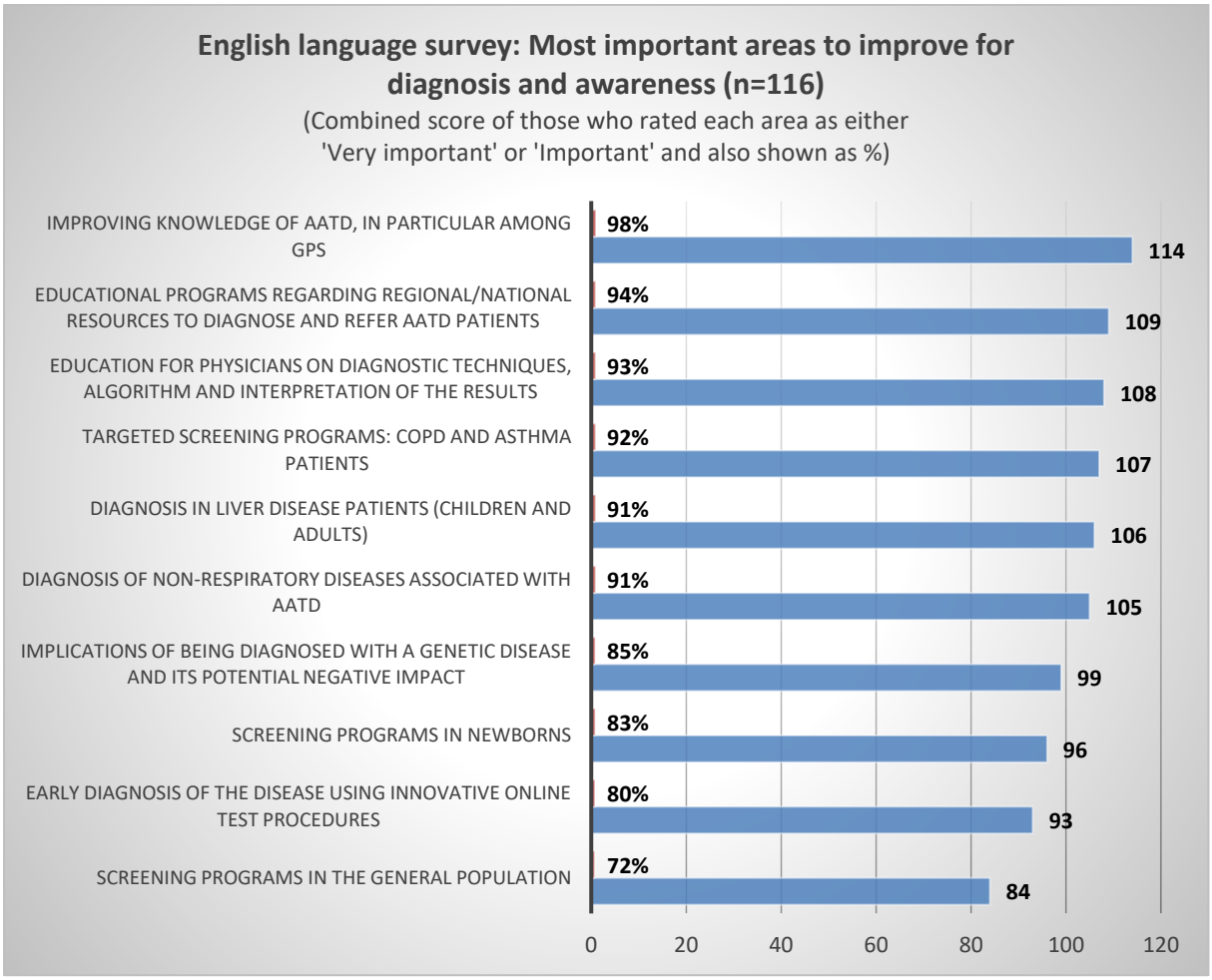
"The benefits of oral treatment versus inhaled treatment".

"Progression of the disease in non-smokers and those in an environment free from smoke/dust /gasses etc."
"Further research into AATD role in the skin. Research into which types/whether all augmentation therapy brands work specifically on panniculitis".
"Make treatments available in the UK for all MZ's heterozygous with lung & liver affected".
"I have had AAT therapy whilst living in Spain and retained the same lung function. I now live in the UK with no access to this and have significant decline in lung function."

Improving diagnosis and awareness of AATD

Respondents were asked to rate a list of areas as to how important each is to improve diagnosis and awareness of AATD. The results in the chart below show the combined scores of those who rated an area as 'Very important' and 'Important'. All but 1 area was rated as 80% or higher with the top 3 most important being:

1. Improving knowledge of AATD, in particular among General Practitioners (98%)
2. Educational programs regarding regional/national resources to diagnose and refer AATD patents (94%)
3. Education for physicians on diagnostic techniques, algorithm, interpretation of results (93%)



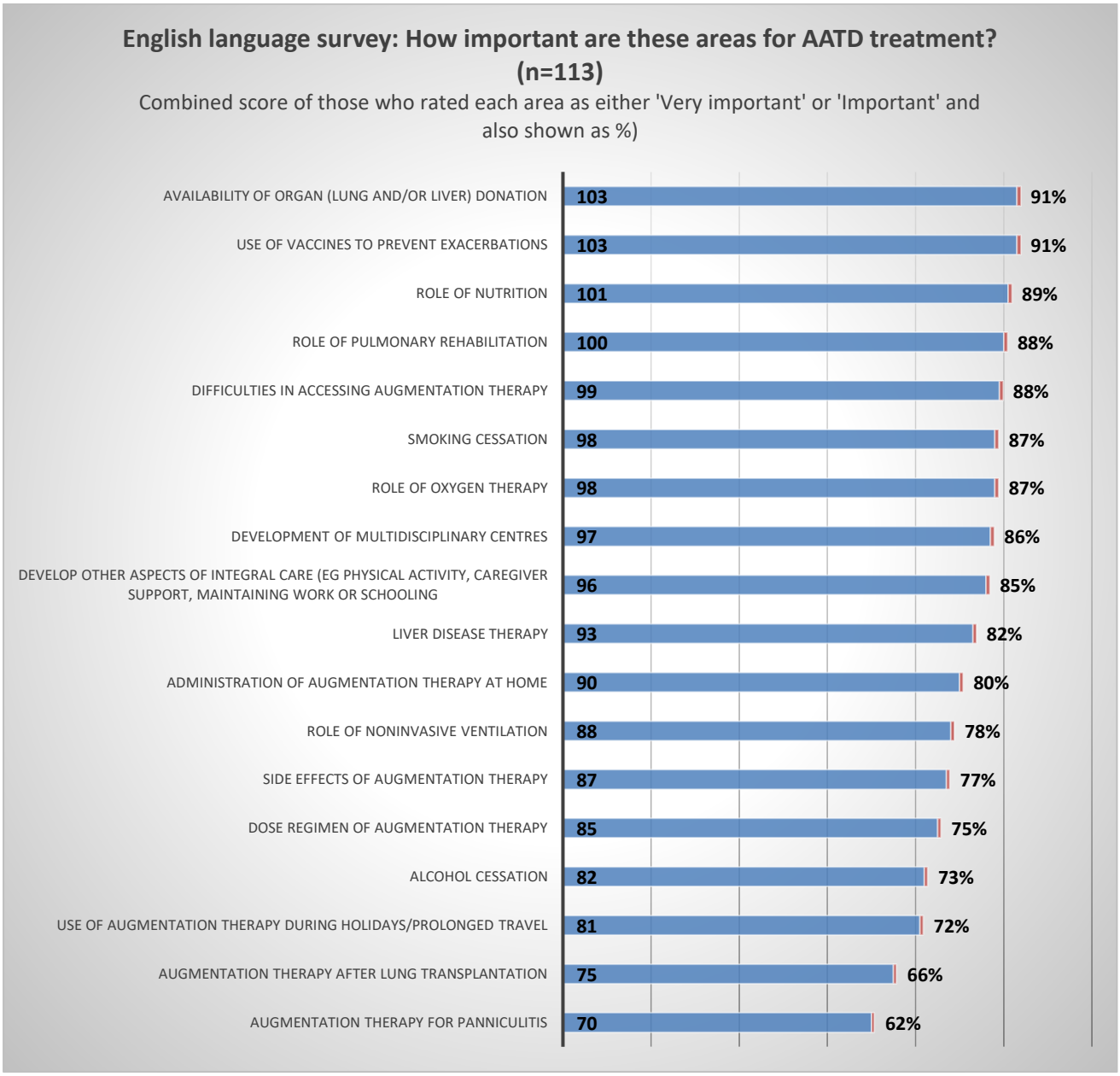
"It is very important that general practitioners are educated because most of them know nothing about it"

"My answers reflect the incredibly difficult first 2-3 months post diagnosis, trying to get the NHS and GP to understand the diagnosis and support me. My own intensive research initially led me to have more knowledge than the GPs I spoke to and only through my persistence, did I finally get to a GP who was happy to learn and refer me to one of the specialist hospitals that I'd discovered existed in the UK, after finding my way to a Facebook support group. After then, I was 'in the system' and this was a massive relief in those early days, post diagnosis."

Improving treatment

Respondents were asked to rate a list of areas as to how important each is to improve treatment of AATD. The results in the chart below show the combined scores of those who rated an area as 'Very important' and 'Important':

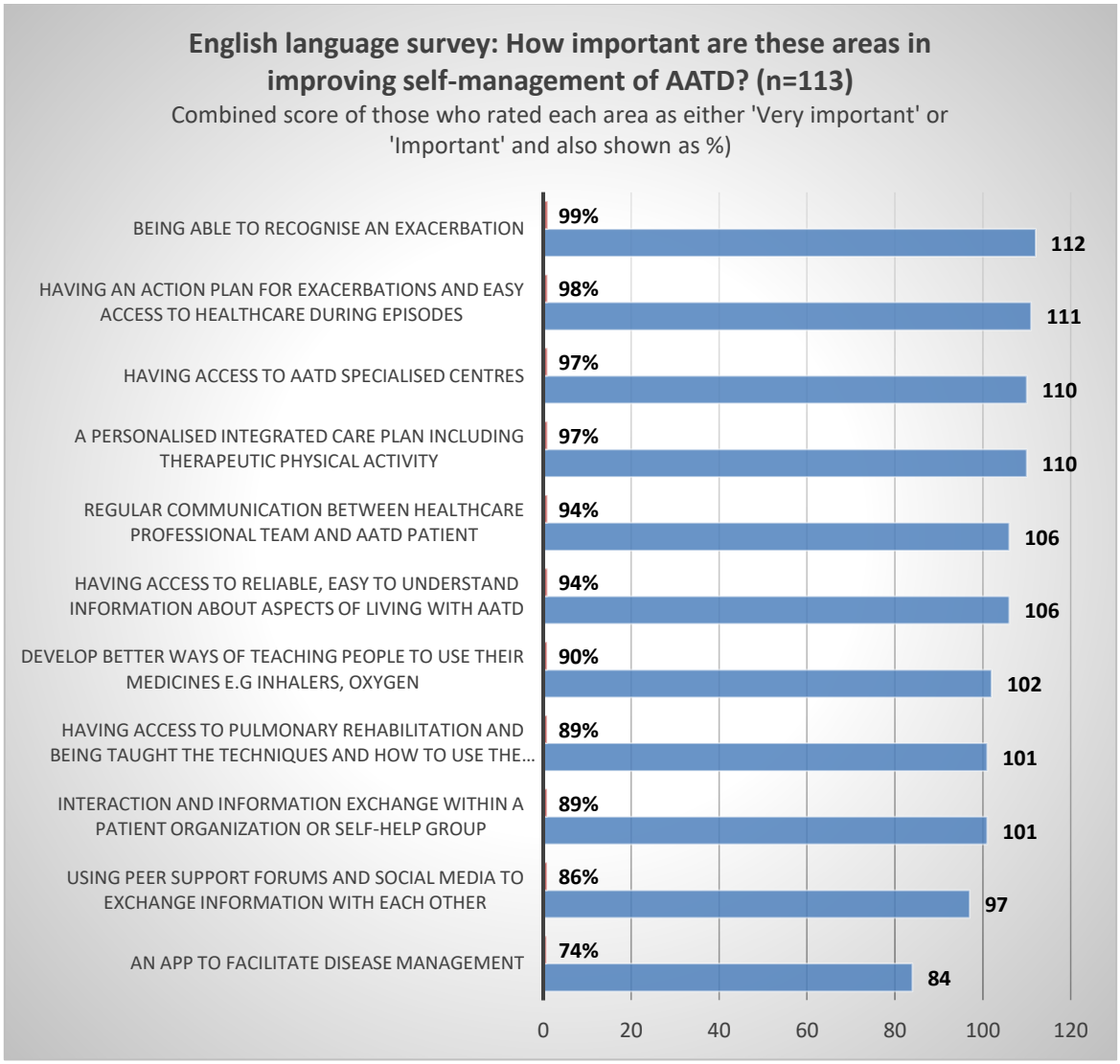
1. Availability of organ (lung and/or liver) donation (91%)
2. Use of vaccines to prevent exacerbations (91%)
3. Role of nutrition (89%)



Self-management and education

Respondents were asked to rate a list of areas as to how important each is to improve self-management of AATD. The results in the chart below show the combined scores of those who rated an area as 'Very important' and 'Important'. The top 3 most important being:

1. Being able to recognise an exacerbation (99%)
2. Having an action plan for exacerbations and easy access to healthcare during episodes (98%)
3. Access to AATD specialised centres (97%) and A personalised integrated care plan including therapeutic physical activity (97%)



"I have used an app called MyCopd which has many features you mention already".
"I have experienced very long wait times for pulmonary rehabilitation. Approximately 6 months for a 6 weeks course with no follow up. I found this to be typical through contact from social media."
"Experts should teach other professionals and share their experience over years so that there is no gap when they retire... New experts have been appointed here but they have zero experience."
"Help in getting medical Insurance when you have AATD that covers all the meds." "Information on getting on the liver transplant list."

Alpha-1 antitrypsin deficiency (AATD)
Patient survey

EARCO CRC

<u>Data comparison</u>:

Responses from those living in countries with AATD therapy reimbursement and those living in countries where AATD therapy is not reimbursed

May 2020

RESPONSES FROM THOSE LIVING IN COUNTRIES WITH AATD THERAPY REIMBURSEMENT AND THOSE LIVING IN COUNTRIES WHERE THERAPY IS NOT REIMBURSED

About the respondents

124 survey responses from people living in the following non-reimbursed countries: Australia, Denmark, Finland, Ireland, Norway, Sweden and United Kingdom were compared with **239** survey responses from people living in the following reimbursed countries: Argentina, Austria, France, Germany, Italy, Portugal, Spain, Switzerland and United States of America.

Who were the respondents?

Non-reimbursed: 86% (n=107) identified as a person diagnosed with AATD and 14% (n=17) identified as a parent, relative or caregiver of someone with AATD.

Reimbursed: 81% (n=194) identified as a person diagnosed with AATD and 19% (n=45) identified as a parent, relative or caregiver of someone with AATD.

Gender

Non-reimbursed: 63% female (n=78), 35% male (n=44) and 2% prefer not to say (n=2)
Reimbursed: 55% female (n=132), 45% male (n=107).

Age

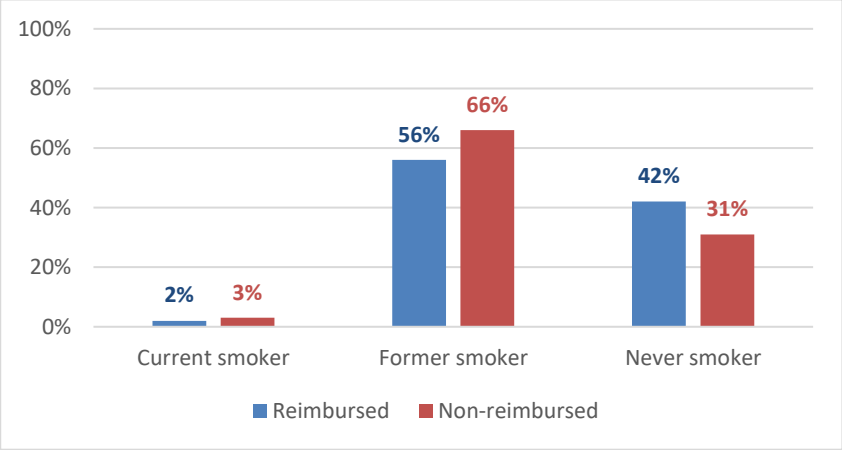
Non-reimbursed: respondents were aged between 1 and 82 years with the mean age of respondents 54 years and the median age 52 years.

Reimbursed: respondents were aged between 1 and 82 years with the mean age 52 years and the median age 48 years.

Smoking

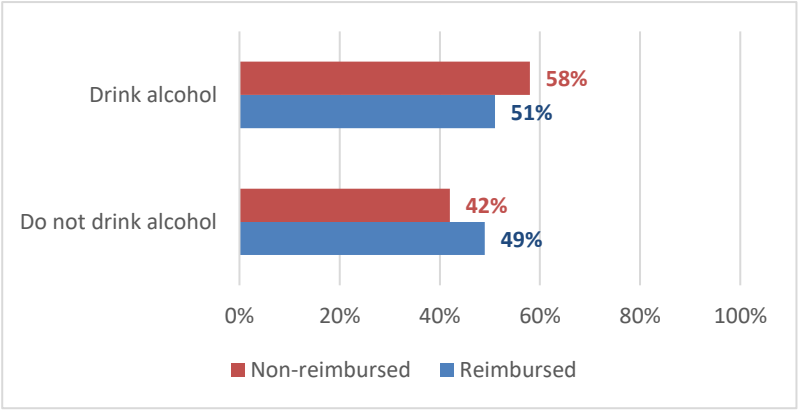
Non-reimbursed (n=119): 66% (n=78) were a former smoker, 31% (n=27) never smoker,
3% (n=4) current smoker.

Reimbursed (n=225): 56% (n=126) were a former smoker, 42% (n=94) never smoker,
2% (n=5) current smoker.



Alcohol

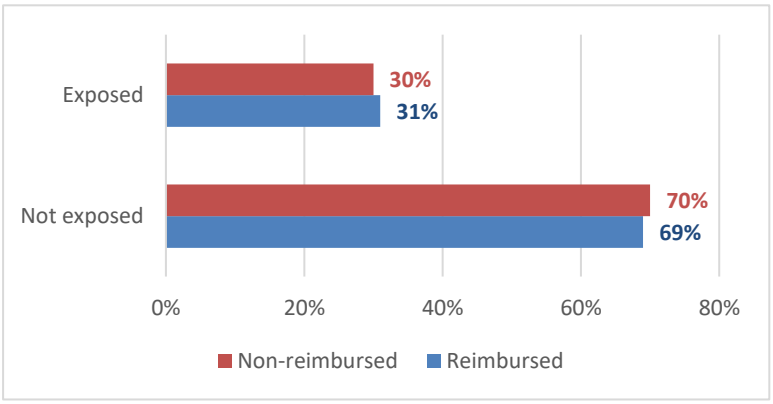
Non-reimbursed (n=119): 58% (n=69) drink alcohol and 42% (n=50) do not drink.
Reimbursed (n=222): 51% (n=113) drink alcohol and 49% (n=109) do not drink.



Environmental exposure

Non-reimbursed (n=119): 70% (n=83) said No they were not exposed to gases, fumes or dust in their professional activities and 30% (n=36) said Yes they were.

Reimbursed (n=225): 69% (n=156) said No they were not exposed to gases, fumes or dust in their professional activities and 31% (n=69) said Yes they were.



Transplants

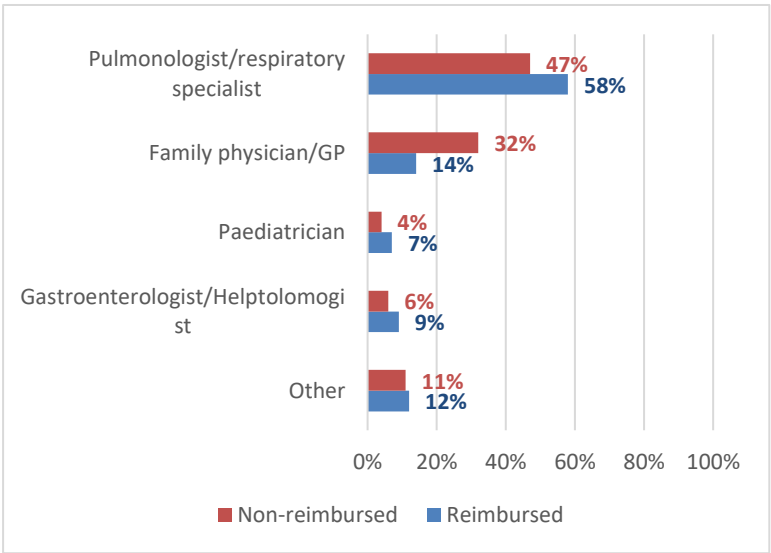
Non-reimbursed (n=119): 1% (n=1) of respondents had a liver transplant and 2% (n=2) respondents had a lung transplant.

Reimbursed (n=225): 1% (n=3) of respondents had a liver transplant and 1% (n=3) had a lung transplant.

Who diagnosed you?

Non-reimbursed (n=119): 47% (n=56) Pulmonologist/respiratory specialist; 32% (n=38) Family physician/GP; 6% (n=7) Gastroenterologist; 4% (n=5) Paediatrician; 11% (n=13) Other.

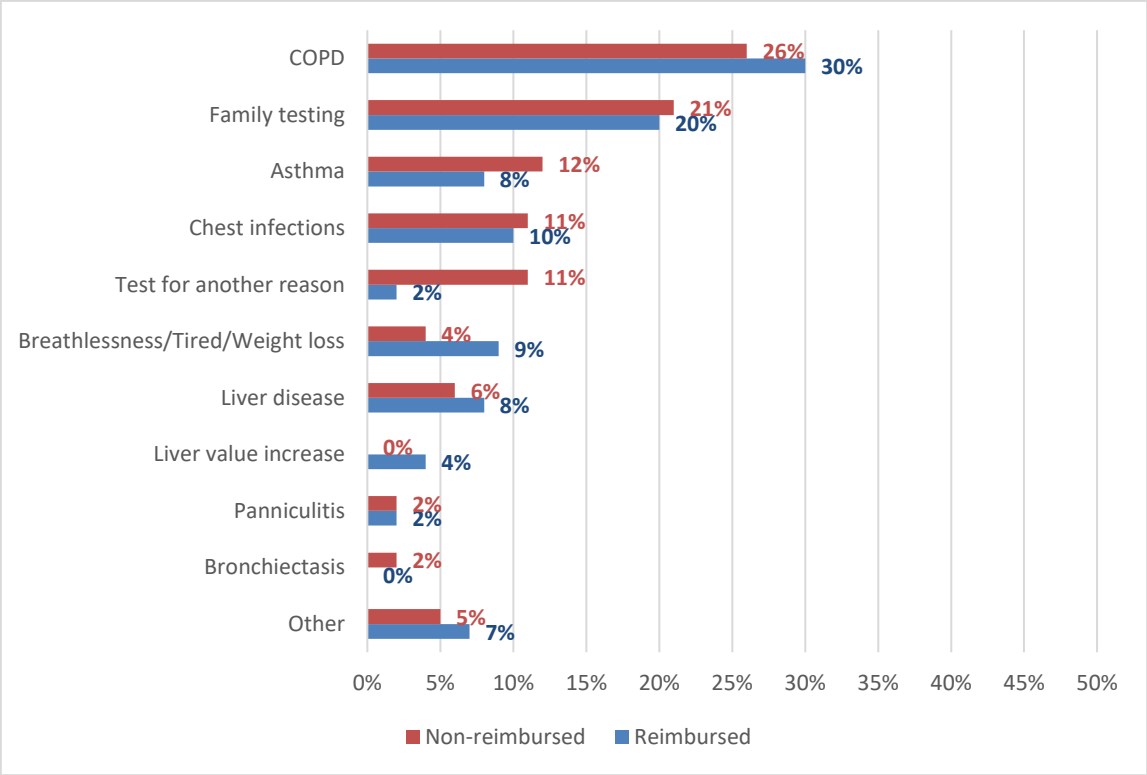
Reimbursed (n=214): 58% (n=125) Pulmonologist/respiratory specialist; 14% (n=29) Family physician/GP; 9% (n=19) Gastroenterologist; 7% (n=14) Paediatrician; 12% (n=27) stated Other.



Reason for diagnosis

Non-reimbursed (n=119): The three most common reasons for diagnosis were: 26% (n=31) COPD; 21% (n=25) Family testing; 12% (n=14) Asthma.

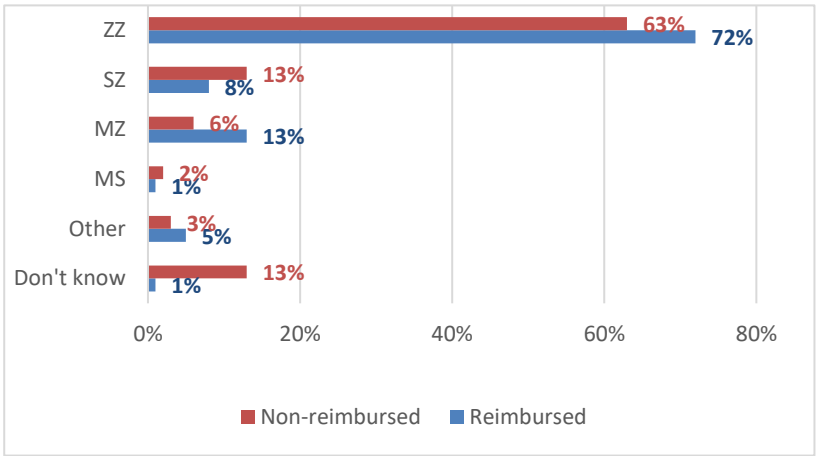
Reimbursed (n=225): The three most common reasons for diagnosis were: 30% (n=68) COPD; 20% (n=45) Family testing; 10% (n=23) Chest infections.



Phenotype

Non-reimbursed (n=119): Most respondents 63% are ZZ (n=75)

Reimbursed (n=224): Most respondents 72% are ZZ (n=161)



How long since diagnosis?

Non-reimbursed (n-119): The length of time since diagnosis ranged from 'less than 1 year' to 45 years with the mean length being 10 years and the median length being 6 years.

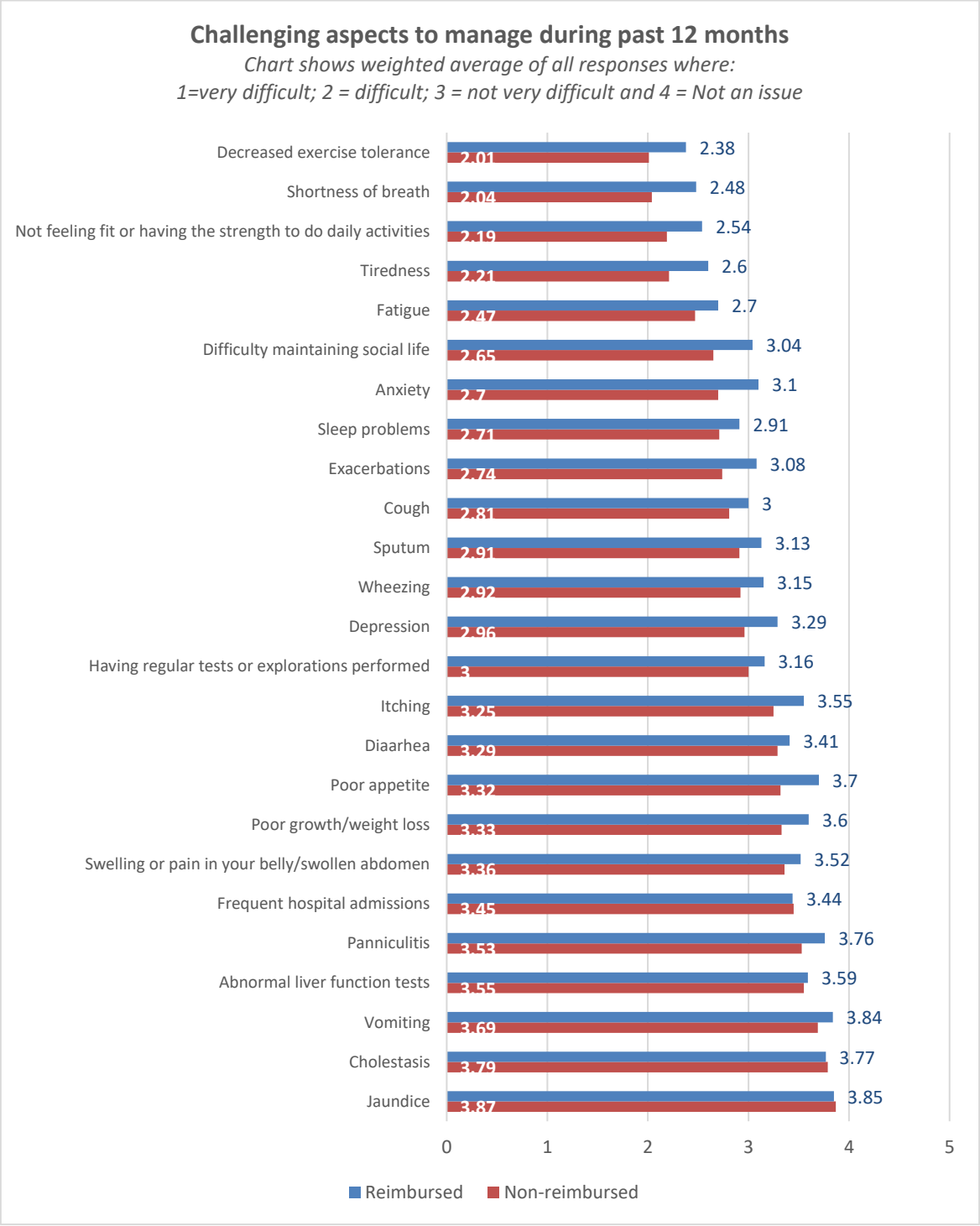
Reimbursed (n=222): The length ranged from 'less than 1 year' to 59 years with the mean length being 11 years and the median length 8 years.

Your experience of AATD

Most challenging aspects to manage during the past 12 months.

Non-reimbursed: 1. Decreased exercise tolerance 2. Shortness of breath 3. Not feeling fit or have strength for daily activities

Reimbursed: 1. Decreased exercise tolerance 2. Shortness of breath 3. Not feeling fit for activities



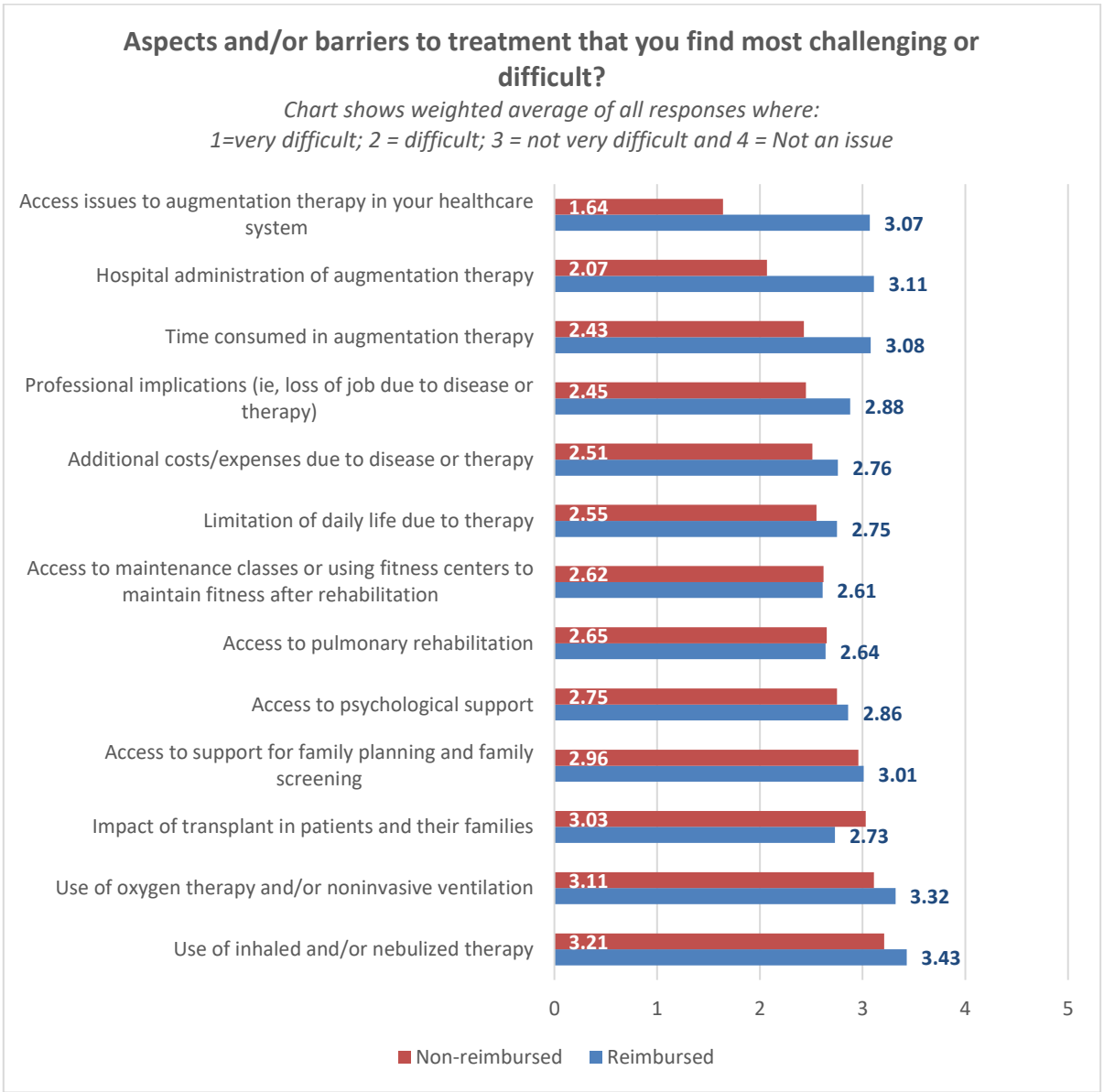
Most challenging aspects/barriers for treatment

Non-reimbursed:

1. Access issues to augmentation therapy in your healthcare system (1.64)
2. Hospital administration of augmentation therapy (2.07)
3. Time consumed in augmentation therapy (2.43)

Reimbursed:

1. Access to maintenance classes / fitness centers to maintain fitness after rehabilitation (2.61)
2. Access to pulmonary rehabilitation (2.64)
3. Impact of transplant in patients and their families (2.73)



Research prioritisation

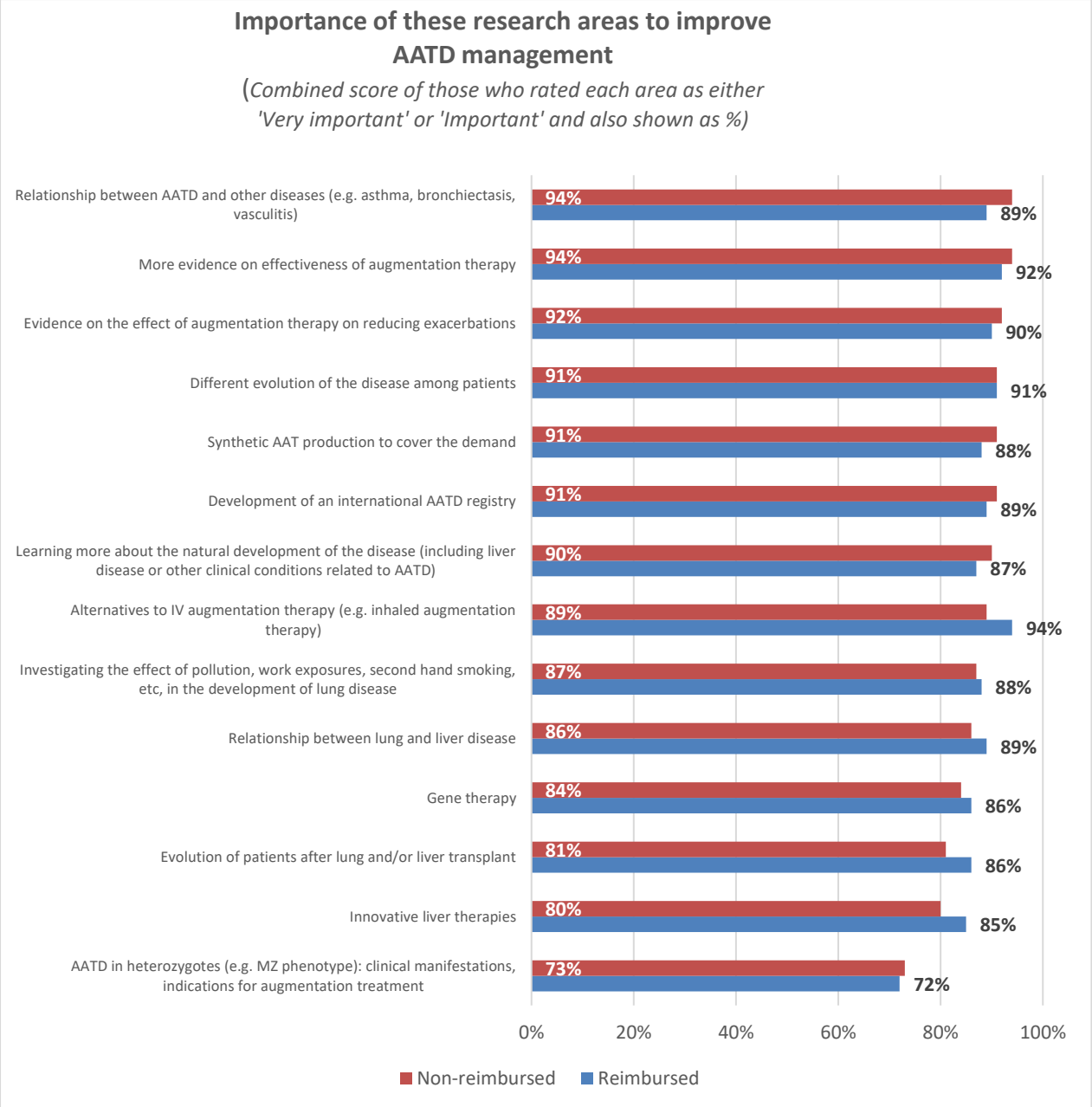
Improving AATD management - The most important research areas:

Non-reimbursed:

1. Relationship between AATD and other diseases (94%)
2. More evidence on effectiveness of Aug Therapy (94%)
3. Evidence on the effect of augmentation therapy on reducing exacerbations (92%)

Reimbursed:

1. Alternatives to IV augmentation therapy (94%)
2. More evidence on effectiveness of augmentation therapy (92%)
3. Different evolution of the disease among patients (91%)



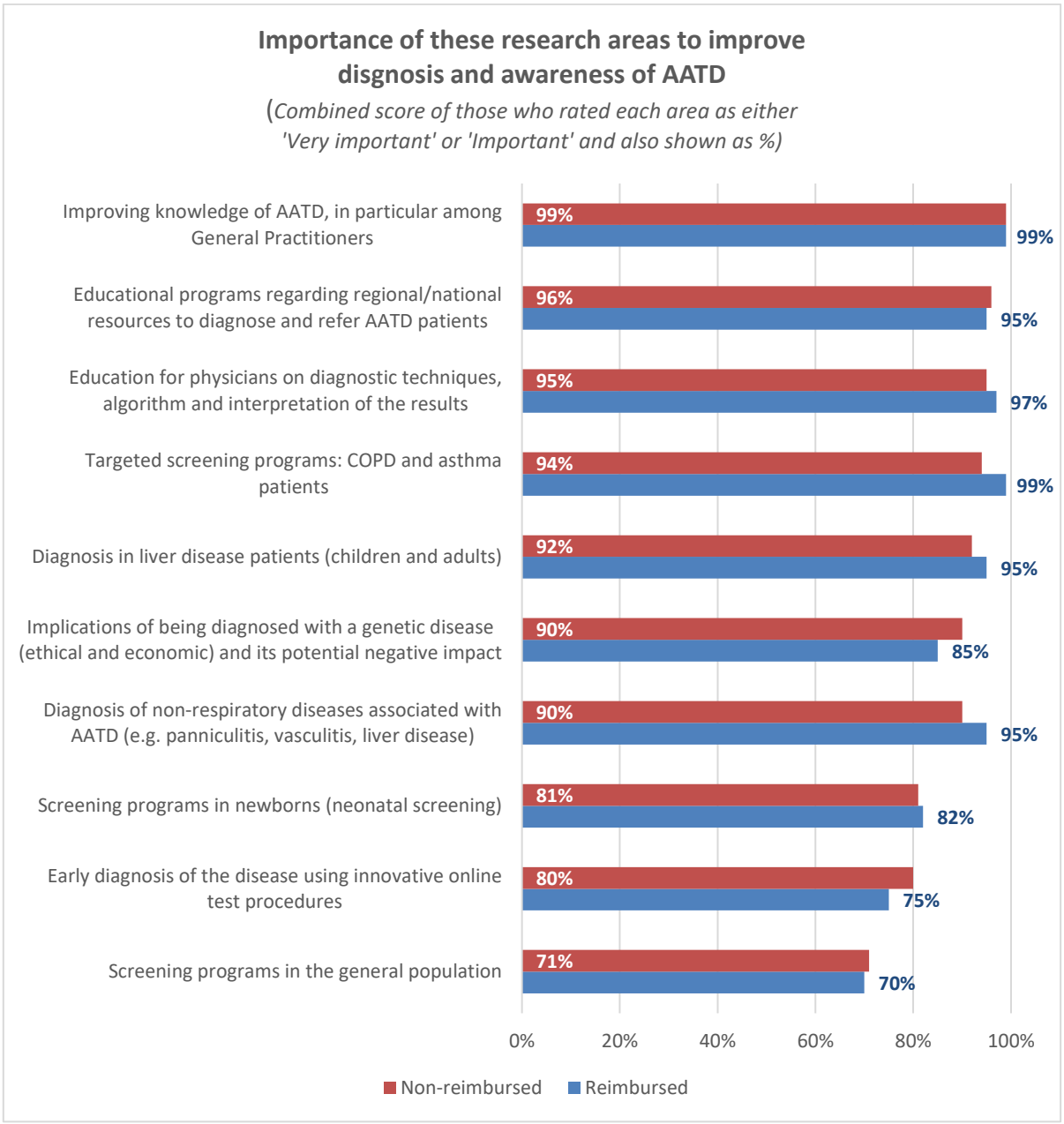
Improving diagnosis and awareness of AATD

Non-reimbursed:

1. Improving knowledge of AATD in particular among GPs (99%)
2. Educational programs for regional/national resources to diagnose/refer patients (96%)
3. Education for physicians on diagnostic techniques, algorithm & results (95%)

Reimbursed:

1. Improving knowledge of AATD in particular among GPs (99%)
2. Targeted screening programs: COPD and Asthma patients (99%)
3. Education for physicians on diagnostic techniques, algorithm & results (97%)



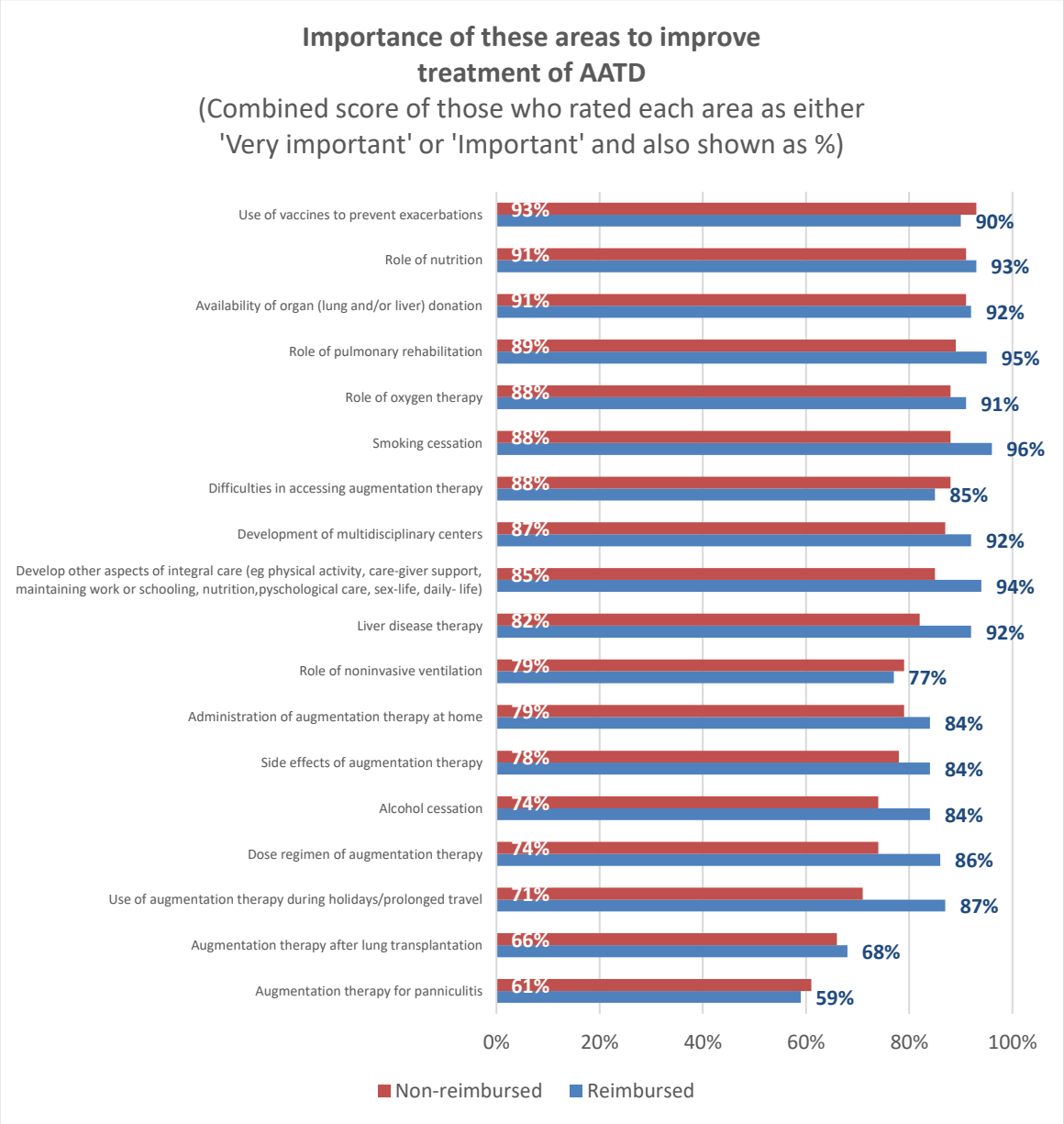
How important do you think it is to improve the following areas for AATD treatment?

Non-reimbursed:

1. Use of vaccines to prevent exacerbations (93%)
2. Role of nutrition / Availability of organ donation (both 91%)
3. Role of pulmonary rehabilitation (89%)

Reimbursed:

1. Smoking cessation (96%)
2. Role of pulmonary rehabilitation (95%)
3. Develop other aspects of integral care (94%)



Self-management and education

Non-reimbursed:

1. Having access to AATD specialized centres (99%)
2. Having access to reliable, easy to understand information about AATD (99%)
3. Having an action plan for exacerbations and easy access to healthcare (99%)

Reimbursed:

1. A personalised integrated care plan including therapeutic physical activity (98%)
2. Being able to recognise an exacerbation (97%)
3. Regular communication between healthcare professional and AATD patient (97%)