BMJ Open

Consensus recommendations on holistic care in hereditary ATTR amyloidosis: an international Delphi survey of patient advocates and multidisciplinary healthcare professionals

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To cite: Obici L, Callaghan R, Ablett J, *et al*. Consensus recommendations on holistic care in hereditary ATTR amyloidosis: an international Delphi survey of patient advocates and multidisciplinary healthcare professionals. *BMJ Open* 2023;**13**:e073130. doi:10.1136/bmjopen-2023-073130

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2023-073130).

Received 28 February 2023
Accepted 28 July 2023

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ABSTRACT

Background Hereditary transthyretin-mediated amyloidosis is a rare, progressive and potentially life-limiting multisystem disease, affecting every aspect of a patient's life.

Objectives This online international Delphi survey aimed to evolve clinical–patient-led practical guidance, to inspire and encourage a holistic approach to care that is managed in specialist settings by multidisciplinary teams and supported by allied healthcare professionals (HCPs) and patient advocacy groups (PAGs).

Design A 14-member joint patient advocate–HCP primary panel was convened including representation from PAGs and key clinical specialties (neurology, cardiology, internal medicine, physiotherapy, clinical psychology, dietetics and specialist nursing). Guidance evolved on the care provision needed to support seven core goals: early diagnosis and treatment; disease monitoring and organisation of care; maintenance of physical and mental health; family-centred care and caregiver support; patient–doctor dialogue; access to social support and social networking.

Participants From June to October 2022, 252 HCPs and 51 PAG representatives from 27 countries were invited to participate in a Delphi survey. Of the 122 respondents who answered at least one survey question, most were HCPs (100, 82%) from specialist centres; the remainder were PAG representatives (22, 18%).

Main outcome measure Both level of agreement and feasibility in practice of each recommendation was tested by two anonymised online Delphi voting rounds.

Results Based on an a priori threshold for consensus of ≥75% agreement, the clinical–patient community endorsed all but one recommendation. However, only 17/49 (35%) recommendations were identified by most HCPs as a core part of routine care; the remainder (32/49 (65%)) were identified as part of core care by <50% of HCPs respondents, or as largely achievable by 30%–45% of HCPs. By comparison, PAGs recorded lower implementation levels.

Conclusions Further consideration is needed on how to evolve multidisciplinary services (supported by allied HCPs and PAGs) to address the complex needs of those affected by this disease.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Led by a primary panel of patient advocates, plus physicians and allied healthcare professionals (HCPs) from specialist centres, this Delphi study aimed to evolve recommendations for the delivery of patient-centred multidisciplinary care based on the needs and priorities of patients and their families affected by hereditary transthyretin-mediated amyloidosis.

⇒ Consensus was sought on 50 draft recommendations from the wider clinical community (mainly neurologists and cardiologists) and representatives from patient advocacy groups invited from 27 countries, who also provided a benchmark assessment on the current application in practice of each recommendation.

⇒ Our survey, translated into French, Spanish and Japanese, also invited anonymised written feedback from patient representatives and HCPs with a special interest in this rare disease.

⇒ The Delphi survey succeeded in recruiting a large panel of international voters; however, regional differences in opinion and practice were not analysed, and the majority of invited participants were from Europe.

INTRODUCTION

Hereditary transthyretin-mediated amyloidosis (ATTRv) is a rare, progressive and highly disabling disease that affects people with pathogenic transthyretin (TTR) gene variants.[1] The accumulation of TTR amyloid fibrils in multiple tissues causes a complex array of symptoms, predominantly in the peripheral nerves (associated with somatic

and autonomic dysfunction), heart (associated with symptoms of restrictive cardiomyopathy and conduction disorders), gastrointestinal tract (associated with diarrhoea, early satiety, vomiting, unintentional weight loss) and, more rarely, in the eyes and kidney.[2] Owing to the complexity and severity of this multisystem disease, every aspect of a patient's life—work, family and social—are affected.[3–5] A coordinated holistic approach to care is needed that considers an individual's clinical, social and spiritual needs and preferences as part of a comprehensive care plan. Through a partnership between patient advocates and healthcare professionals (HCPs), this study aimed to inform measures to overcome the inequalities in healthcare provision, to enhance shared decision-making and to promote the development of personalised care. However, unlike similar initiatives in other chronic diseases,[6–8] ATTRv management requires coordinated support from multiple specialties beyond the core multidisciplinary team (MDT). Currently, care is coordinated by specialist MDTs (including neurology, cardiology, internal medicine and nurse specialists), who may be located at regional or national centres.[9–11] Patients may also be referred to other allied healthcare specialists, including genetic services, ophthalmology, physiotherapy, clinical psychology, nutrition and dietetic service and occupational therapy.

Like other rare diseases, there are no universal standards for the coordinated holistic care of patients with ATTRv amyloidosis.[12 13] As patients and their families learn to become experts in their own condition, they often need the support of the healthcare team to guide decisions on their care.[14 15] Clinical practice varies between countries, as do the resources to diagnose and manage patients with ATTRv amyloidosis.[16] In 2019, the patient advocacy group (PAG) coalition Amyloidosis Alliance called for an expansion of local services, acknowledging the need for a broader and more holistic approach to health and social care, to reduce the burden of disease for patients and their families.[17]

We report the results of an international study using modified Delphi methodology[18 19] for the development of practical guidance to inspire and encourage a holistic approach to care that is managed by specialists in a multidisciplinary setting and supported by allied HCPs and PAGs. This paper outlines the evolution of the clinical–patient representative-led recommendations and presents their final iteration based on findings from an international Delphi survey of representatives from the clinical and patient community. Both the validity (level of agreement) as well as the feasibility of each recommendation in practice is explored.

METHODS

Study design

Delphi is an iterative process that uses rounds of anonymised voting, leading to a convergence of experts' judgements and opinion on a proposed statement/recommendation.[18] We used a modified Delphi methodology which included the following three steps (outlined in figure 1): (1) formation of a Primary Consensus Panel for the origination and agreement of draft recommendations using anonymised online voting (Voting round 1); (2) anonymised online voting on translated draft recommendations from the wider international clinical community (Voting round 2) and (3) discussion and modification of recommendations by Primary Consensus Panel for final vote by the international panel if consensus was not reached (Voting round 3). The aim was to achieve consensus on recommendations for the holistic care of people with ATTRv amyloidosis. Detailed descriptions of the various stages of the consensus-building process are provided in online supplemental appendix S1.

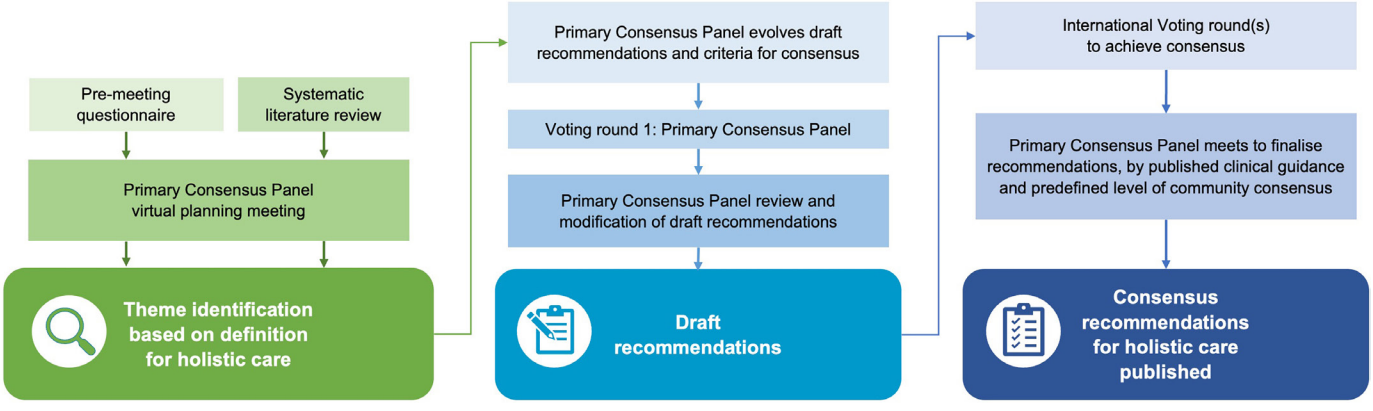

Figure 1 Modified Delphi methodology to build consensus on recommendations for the holistic care of people with ATTRv amyloidosis. Modified Delphi methodology was used to achieve consensus, which included three steps: (1) formation of a Primary Consensus Panel for the origination and agreement of draft recommendations using anonymised online voting (Voting round 1); (2) anonymised online voting on translated draft recommendations from the wider international clinical community (Voting round 2); (3) discussion and modification of recommendations by Primary Consensus Panel for final vote by the international panel if consensus was not reached (Voting round 3). Detailed descriptions of the various stages of the consensus-building process are provided in online supplemental appendix S1. ATTRv, hereditary transthyretin-mediated amyloidosis.

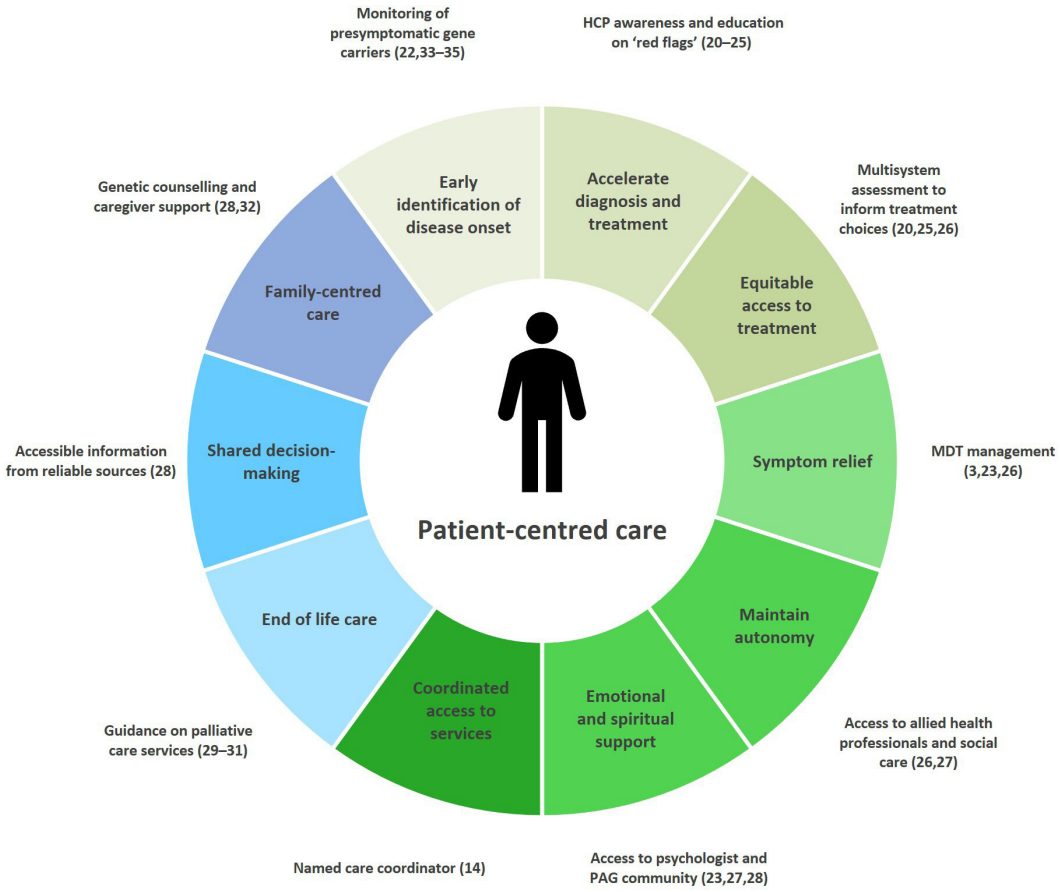

Figure 2 Opportunities and challenges for the delivery of care for patients with ATTRv amyloidosis and their caregivers. ATTRv, hereditary transthyretin-mediated amyloidosis; HCP, healthcare professional; MDT, multidisciplinary team.

Primary Consensus Panel and scope for consensus

To ensure the draft recommendations reflected the priorities of patients as well as the clinical experience of the MDT, input was sought from a Primary Consensus Panel (co-chaired by Dr Laura Obici, Internist, Italy, and Rosaline Callaghan, PAG representative for Northern Ireland and Republic of Ireland) and comprising both PAG representatives and members of the multidisciplinary care team (neurology, cardiology, physiotherapy, psychology, dietetics and specialist nursing). In the initial stages, the 14-member joint patient advocate–HCP Primary Consensus Panel convened to consider the care provision to support seven core goals on: (1) early diagnosis and access to treatment; (2) disease monitoring and organisation of care; (3) maintenance of physical and mental health, and quality of life; (4) family-centred care and caregiver support; (5) patient–HCP dialogue and shared decision-making; (6) access to community and social support and (7) spiritual support and social networking. Discussions were enriched by the findings from a literature review (prepared in advance of the first Primary Consensus Panel meeting; for details, see online supplemental appendix S1). All members of the Primary Consensus Panel took an active role in identifying the challenges and opportunities which could be addressed by the recommendations (figure 2)[3 14 20–35] and in the writing and reviewing of the recommendations, using published evidence/guidelines (where available) to support each recommendation. All members of the Primary Consensus Panel were involved in the writing and review of this paper.

Statement development

For each of the core themes, responsibility was assigned to a writing group of 3–4 panel members (including both PAG representatives and HCPs) who drafted the recommendations reflecting on the goals and considerations for optimal service design (figure 3). The panel then convened to review the recommendations before a consensus was established by the primary consensus panel using an anonymised online Delphi survey (Voting round 1). To help improve accessibility to the online Delphi survey, the final iteration of the draft recommendations from the primary consensus panel were translated into French, Spanish and Japanese.

International voting panel

Nominations for the international voting panel (ie, clinicians and PAG representatives with a special interest in this rare disease) were provided by the Primary Consensus Panel and national PAG representatives. In total, 252 HCPs with a special interest in the management of ATTRv

Figure 3 Considerations for the delivery of care for patients with ATTRv amyloidosis and their caregivers. ATTRv, hereditary transthyretin-mediated amyloidosis; HCP, healthcare professional; QoL, quality of life.

amyloidosis and 51 PAG representatives from 27 countries were invited to take part in the Delphi survey (online supplemental figure S1). Prior to starting the survey, all participants were required to provide consent for the analysis of their anonymised answers.

Online Delphi survey design and analysis of the data

Consensus on the draft recommendations for holistic care was assessed using an anonymised online voting questionnaire. For each recommendation, the questionnaire tested two outcomes. First, it tested the level of agreement for each recommendation based on a six-point Likert scale: '1', strongly agree; '2', agree; '3', agree with minor changes; '4', neither agree nor disagree; '5', disagree/strongly disagree and '6', don't know. Second, voters were asked to assess the current level of implementation of each recommendation in their practice/service setting, based on the following criteria: '1', core—recommendation is part of current practice; '2', achievable—recommendation is attainable with currently available resources; '3', aspirational—the recommendation is only attainable with further funding or reorganisation of care and '4', not applicable. Voters were also given the opportunity to provide anonymised written feedback on each recommendation.

An a priori threshold for consensus from the international clinical community, was defined as at least 75% group agreement (ie strongly agree or agree) for each recommendation. This threshold aligns with the median threshold identified from a systematic literature review of Delphi consensus studies.[36] The level of consensus on each recommendation was analysed based on votes from all respondents and their implementation based on the votes from HCPs. A comparison was also made between the votes from HCPs and PAG representatives to identify any differences in either the level of consensus or the application of recommendations in practice (evaluated by the core theme and each individual recommendation).

Patient and public involvement (based on Guidance for Reporting Involvement of Patients and the Public [GRIPP])

Representatives from five European ATTR Amyloidosis PAGs (most of whom are patients) were invited to join the Primary Consensus Panel and were involved as research partners in all aspects of the Delphi survey. This included taking part in all the consensus workshops, identifying the scope, opportunities and challenges for the delivery of holistic care to support patients and families affected by ATTRv amyloidosis and writing the draft recommendations. The Primary Consensus Panel, along with representatives from many other national PAGs, identified the participants for the Delphi survey (including HCPs and PAG representatives from 27 countries). PAG representatives on the Primary Consensus Panel helped pilot the electronic survey for the first phase of the Delphi survey consensus process and helped check the comprehension of the recommendations from the lay perspective, hence improving the response rate to the Delphi from PAGs.

They also worked with HCPs on the Primary Panel to review comments from the Delphi survey round. The PAG representatives contributed to development of the paper and are coauthors. The final recommendations will be disseminated to all study participants who asked for their institution to be acknowledged on the paper (including PAGs), via email. The authors will disseminate via conference presentations the findings from this Delphi survey.

RESULTS

Characteristics of respondents to the international Delphi survey

Between 1 June 2022 and 6 October 2022, 122 people (100 HCPs and 22 PAG representatives) responded to an invitation from the panel co-chairs and consented to take part in the Delphi survey and voted on at least one of the recommendations. The response rates from invited HCPs and PAG representatives were similar (100 of 252 (40%) invited HCPs and 22 of 51 (43%) invited PAG representatives). Most HCPs (88 of 100, 88%) were from specialist centres that diagnose or treat patients with ATTRv amyloidosis and the remainder were from referral centres. Neurologists represented 37% (45) of total voting panel, cardiologists (28, 23%), internists (8, 7%), amyloid specialists (7, 6%), allied HCPs (7, 6%) and others (5, 4%). A consistently high number of respondents (average 91%) voted on each consensus statement as well as on the 'application in practice' for each statement (90% and 91% of HCPs and PAGs, respectively). Respondents dedicated an average of 22 min to completing the survey and providing written feedback.

Draft statements

Overall, 50 recommendations based on seven core themes were drafted by separate working groups, each made up of 3–4 members from the Primary Consensus Panel. Thereafter, the Primary Consensus Panel participated in a preliminary round of voting (Voting round 1) to test the level of agreement on the recommendations among the panel members. Consensus was reached on all recommendations; consequently, no significant updates were made to the draft recommendations after Voting round 1. Most recommendations (78%) related to the first three themes: (1) early diagnosis and access to treatment (8 (16%) of total recommendations); (2) disease monitoring and organisation of care (13 (26%)) and (3) relief from symptoms and the stress of illness through measures to maintain physical and mental health (18 (36%)). The remaining recommendations (22%) provided guidance on the final four themes: (4) family-centred care and caregiver support (three recommendations); (5) patient–HCP dialogue and shared decision-making (three recommendations); (6) access to community social support (two recommendations) and (7) spiritual support and social networking (three recommendations) (tables 1 and 2).

Results from online voting

Consensus

Based on the a priori threshold for consensus of ≥75% group agreement (ie, strongly agree or agree), the international HCP–patient community endorsed all but one of the Primary Consensus Panel's recommendations (tables 1 and 2, online supplemental figure S2). The only recommendation not endorsed by all voters was the role of complementary therapies as part of self-care (recommendation 3.6.1; 70.5% agreement (all voters) and 79% (voters representing PAGs)). Although all-voter agreement on this recommendation fell just short of the 75% threshold for consensus, amendment and a revote on this recommendation was not considered necessary by the Primary Consensus Panel, as complementary medicines generally fall outside the remit of mainstream clinical care, but might be considered by PAGs when discussing self-care with patients and families (current application in practice: 37% according to PAG voters). Consequently, there was no requirement for a third voting round.

Application in practice

Analysis of the application in practice for each recommendation was based on the votes from HCPs (tables 1 and 2). Only 17/49 (35%) of the recommendations were identified by most HCPs as a core part of routine care; the remaining recommendations (32/49 (65%)) were identified as either part of core care by <50% of HCPs respondents, or as largely achievable with currently available resources by 30%–45% of HCPs (tables 1 and 2, online supplemental figure S3). By comparison, PAGs recorded lower implementation levels. Unlike the consensus voting, where there was agreement on almost all recommendations by HCPs (data not shown), the proportion of HCPs voters who considered the recommendations to be already a core part of everyday practice varied widely, from high level of current application in practice (≥66% HCP voters) for 6 of 8 recommendations on early diagnosis and intervention; to a moderate (≥50% to <66%) or high level of current application in practice for 7 of 13 recommendations on disease monitoring and organisation of care. In addition, between ≥50% and <66% of HCPs considered the following to be part of current care: the assessment and referral of patients to a nutritionist (recommendation 3.5.1); information for patients on the hereditary nature of the disease at diagnosis (recommendation 6.2); family-centred follow-up for genetic counselling and testing (recommendation 4.1); and the discussion with patients on the likely course of the disease and the care plan (recommendation 5.1) (tables 1 and 2, online supplemental figure S3). The reasons and implications for these findings are explored in more detail in the Discussion section.

Comparison of votes from HCPs and PAGs

Comparison of the voting by HCPs and PAG representatives identified a high level of concordance on recommendations grouped by core theme (figure 4A), but PAG representatives reported a lower implementation in practice for all core themes except for occupational therapy, psychological support and spiritual support/social networking (figure 4B).

Table 1 Delphi survey results for recommendations 1.0–3.2 on the level of consensus for the recommendations (based on all voters; n=122) and their application in practice as either a 'core' or 'achievable' part of care (based on votes from HCPs; n=100)

Recommendations	Consensus* (strongly agree) —all voters	Application core (or achievable) —HCPs only	Published recommendation (ref)
1.0 Early diagnosis and access to treatment			
1.1 It should be mandatory to offer genetic testing (with genetic counselling) to confirm the diagnosis of symptomatic ATTRv amyloidosis.	91.0% (76.2%)	69.4% (18.4%)	25
1.2 In patients with a TTR variant and a serum and/or urinary monoclonal gammopathy, the type of amyloid deposits should always be identified by immunohistochemistry or proteomics.	79.8% (54.6%)	46.4% (30.9%)	46
1.3 If a TTR variant is identified, follow-up genetic counselling is recommended to discuss the implications for the patient and their family and to support presymptomatic genetic testing of at-risk family members, as well as provide advice on prenatal testing.	97.5% (75.8%)	67.0% (23.7%)	25
1.4 Comprehensive baseline assessments (eg, neurological, cardiac, ophthalmic) should be mandatory, shortly after diagnosis, to identify disease burden and guide decisions on treatment (both pharmacological and non-pharmacological).	93.3% (77.3%)	71.4% (19.4%)	25
1.5 Treatment decisions should be informed by the latest evidence, discussion within the multidisciplinary team (as needed) and made jointly with the needs and wishes of the patient.	100.0% (85.8%)	75.5% (13.3%)	25
1.6 Where available, disease-modifying treatments should be initiated immediately after diagnosis in all eligible patients.	91.7% (75.8%)	66.3% (17.4%)	25 47
1.7 Timely and regular multidisciplinary monitoring of asymptomatic gene carriers should be undertaken to identify and treat the first signs of disease.	97.5% (77.5%)	66.0% (16.5%)	25 48
1.8 Ensure patients and their support networks are provided with adequate information and education, using patient-friendly materials and communication, to ensure they understand their diagnosis and options for management of their disease.	98.3% (80.8%)	48.5% (37.1%)	N/A
2.0 Disease monitoring and organisation of care			
2.1 Multidisciplinary follow-up should be tailored for each patient according to their signs and symptoms and expected disease course (consistent with their genotype).	95.7% (72.7%)	68.4% (21.1%)	25 26 49
2.2 Variability in penetrance, symptoms and course of ATTRv amyloidosis requires that all patients, regardless of variant status, undergo regular, standardised neurological and cardiac assessments (as a minimum) to capture somatic and autonomic neuropathies as well as evolving cardiac manifestations.	90.6% (66.7%)	65.3% (19.0%)	50 51
2.3 Patients' care should be managed at centres with the facilities and expertise to provide multidisciplinary care with coordinated access to other specialist services as needed.	98.3% (78.6%)	68.4% (17.9%)	25 26 49
2.4 The minimum level of coordinated multidisciplinary support team should comprise a neurologist and a cardiologist, a genetic counsellor, a specialist nurse and an ophthalmologist. Other specialists such as gastroenterologists, nutritionists, psychologists, physical therapists (or physiotherapist), occupational therapists, nurses, nephrologists, urologists and primary care physicians should be consulted as needed.	82.1% (51.3%)	51.1% (27.7%)	34
2.5 Where possible, changes in the disease course should be confirmed using both subjective assessments and complimentary objective tests taken at least 6 months apart.	88.9% (50.4%)	56.4% (30.9%)	46
2.6 Patients should be followed up and monitored consistently at the same centre(s) to minimise subjective bias in the reporting of signs and symptoms of progression.	92.2% (58.6%)	58.5% (23.4%)	10 46
2.7 A minimum follow-up interval of 6–9 months for all disease manifestations should be considered, and follow-up time adjusted based on the patient's evolving symptoms and treatment.	88.8% (53.5%)	61.3% (24.7%)	38 52

Continued

Table 1 Continued

Recommendations	Consensus* (strongly agree) —all voters	Application core (or achievable) —HCPs only	Published recommendation (ref)
2.8 Patients should be offered an interim review (telemedicine if in-person review is not possible) should they notice a worsening of symptoms or development of a new symptom in between scheduled in-person clinic visits.	93.2% (61.5%)	34.8% (41.3%)	34
2.9 Structured disease education with a member of the specialist team (eg, specialist physician or nurse) should begin within 6 months after diagnosis to promote self-efficacy and empower patients to self-monitor and self-advocate. This should also be offered to gene carriers.	88.9% (51.3%)	28.7% (36.2%)	N/A
2.10 Specialist regional (or national) centres should help facilitate access to other specialist services, for example, pain management programmes, sexual health services and psychological services, as a holistic package of care for symptom management.	95.7% (59.5%)	24.2% (44.2%)	10
2.11 Local support and services should be identified near patients' homes to help support long-term care.	94.9% (54.7%)	23.4% (38.3%)	10
2.12 A care coordinator should be identified within a specialist centre who can oversee each patient's care plan and act as a key contact point for patients and their families, and the multidisciplinary team.	93.2% (57.3%)	33.0% (34.0%)	N/A
2.13 Specialist centres should offer nurse specialists and allied healthcare professionals, including primary care practitioners, training to increase awareness of the specific needs of people with ATTRv amyloidosis and their families and to help implement self-care programmes.	90.6% (51.3%)	14.0% (38.7%)	N/A
3.0 Maintenance of physical and mental health			
3.0 Specialist centres should support the evolution of local or regional services (including educational programmes) to address the needs of patients with complex healthcare needs, such as ATTRv amyloidosis.	92.7% (50.5%)	15.7% (37.1%)	N/A
3.1 Physiotherapy			
3.1.1 Early assessment (including sensory and motor evaluation) should be conducted to evaluate patients' rehabilitation or self-rehabilitation needs, and to design and provide appropriate programmes.	96.4% (59.1%)	31.8% (33.0%)	53
3.1.2 Sensory and motor exercise self-education programmes should be adapted to the physical (and mental) capabilities of each patient, to help patients maintain stamina and to improve cardiorespiratory fitness and exercise tolerance.	94.5% (58.2%)	21.6% (37.5%)	N/A
3.1.3 Physiotherapists should advise patients on sensorimotor self-education programmes to help improve strength and dexterity (fine motor skills) in their hand and arm movements.	89.1% (54.6%)	17.1% (38.6%)	N/A
3.1.4 Where necessary, independent living aids and mobility aids should be offered to help patients maintain their autonomy.	97.2% (75.9%)	37.5% (31.8%)	N/A
3.2 Occupational therapy			
3.2.1 Patients should be referred for assessment for occupational therapy support at diagnosis or when symptoms affecting safety, mobility or independence appear.	95.4% (62.4%)	25.3% (35.6%)	N/A
3.2.2 Where necessary, technical and/or mechanical aids and adaptations should be made available to help maintain autonomy and mobility both inside and outside of the home.	99.1% (67.0%)	33.0% (42.1%)	N/A
3.2.3 Educational materials should be provided to employers and other relevant contacts, describing the diagnosis and burden of ATTRv amyloidosis for the patient, in order to help raise awareness and understanding of the disease.	91.7% (56.0%)	21.6% (36.4%)	N/A

Application in practice as a core part of care: High: ≥66% of HCPs. Moderate: ≥50%–<66%. Low: ≥25%–<50% of HCPs. Very low: 25% of HCPs.
*Defined as 'strongly agree' and 'agree' responses.
ATTRv, hereditary transthyretin-mediated amyloidosis; HCP, healthcare professional; N/A, not available; TTR, transthyretin.

Table 2 Delphi survey results for recommendations 3.3–7.3 on the level of consensus for the recommendations (based on all voters; n=122) and their application in practice as either a 'core' or 'achievable' part of care (based on votes from HCPs; n=100)

Recommendations	Consensus* (strongly agree) —all voters	Application core (or achievable) —HCPs only	Published recommendation (ref)
3.3 Podiatry			
3.3.1 Patients with peripheral neuropathy affecting the feet should be referred for podiatry assessment at diagnosis or when symptoms of impaired mobility appear.	84.1% (49.5%)	20.7% (39.1%)	N/A
3.3.2 Podiatrists should monitor the trophic skin changes on the feet and advise on suitable insoles or shoes with adapted moulds, according to the needs of each patient.	83.2% (44.9%)	16.1% (40.2%)	N/A
3.4 Psychological support			
3.4.1 Patients should be given the option of referral to psychological services for assessment and support shortly after diagnosis.	98.1% (67.9%)	26.4% (43.7%)	N/A
3.4.2 Patients, family members and caregivers should be offered psychological support, especially during 'moments of crisis', for example, before and after pre-symptomatic genetic testing of at-risk family members, and when symptoms progress, resulting in a significant impact on patients' quality of life.	97.2% (67.3%)	24.1% (34.5%)	N/A
3.4.3 Whenever possible, collaboration between psychologists and specialist centres should be encouraged to integrate psychological aspects of care and to screen patients for psychological needs.	92.5% (55.7%)	16.1% (41.4%)	N/A
3.5 Nutrition			
3.5.1 Patients should be regularly assessed to identify the red flags (unintentional weight loss; upper GI symptoms such as early satiety, nausea and vomiting; lower GI symptoms such as constipation, alternating diarrhoea/constipation, diarrhoea and faecal incontinence) for referral and early intervention by an expert nutritionist.	94.3% (75.5%)	52.3% (33.7%)	N/A
3.5.2 Nutritionists should use assessment tools, such as the Subjective Global Assessment, Mini Nutritional Assessment, modified body mass index and the EQ-5D Index 1 to evaluate the degree of malnutrition and existing cachexia.	80.2% (44.3%)	24.4% (40.7%)	N/A
3.5.3 In patients with low body mass index and low muscle mass, a combination of nutritional intervention and physical therapy should be considered; in particular, protein intake should be increased in combination with specific (tailored) rehabilitation programmes to maintain muscle strength, physical functioning and metabolic activity.	85.9% (57.6%)	25.6% (41.9%)	N/A
3.5.4 Whenever possible, collaboration between expert nutritionists and physical therapists should be encouraged.	87.7% (42.5%)	12.9% (43.5%)	N/A
3.6 Self-care			
3.6.1 Care teams/coordinators should explore with patients the range of complementary therapies and local services or groups available to alleviate the physical and emotional impact of living with ATTRv amyloidosis. These could include adjuncts such as mindfulness, relaxation, yoga, massage, hydrotherapy, Tai χ, Qi Gong, Pilates or other services deemed suitable for self-care.	70.5% (33.3%)	4.7% (20.9%)	N/A
4 Family-centred care and caregiver support			
4.1 Adult family members (18 years of age and older) should be offered cascade genetic testing with mandatory genetic counselling before and after genetic testing.	89.6% (60.4%)	57.7% (24.7%)	N/A
4.2 Care teams should encourage open discussion with patients and caregivers on the need for home support for the patient.	96.2% (59.1%)	36.1% (45.4%)	N/A
4.3 Family members/caregivers should be involved in rehabilitation and physiotherapy sessions, so that they can provide extra support and gain insights into the progress and general well-being of the patient.	84.0% (39.6%)	14.0% (45.4%)	N/A
5 Patient–HCP dialogue and shared decision-making			

Continued

Table 2 Continued

Recommendations	Consensus* (strongly agree) —all voters	Application core (or achievable) —HCPs only	Published recommendation (ref)
5.1 Care teams should encourage open discussion with patients and their families on the hereditary nature of the disease, the likely course of the disease (including likely cause(s) of death, as appropriate), so that patients and families can plan for the future.	96.2% (65.7%)	54.7% (27.9%)	N/A
5.2 Care teams should identify the patients' and caregivers' short-term and long-term priorities for their disease management, including a discussion on their life goals, to ensure this is central to all decision-making.	92.5% (50.9%)	36.1% (41.9%)	N/A
5.3 Care teams should encourage patients and families to ask questions and help overcome any barriers associated with difficult and embarrassing issues.	98.1% (65.1%)	46.5% (37.2%)	N/A
6.0 Access to community and social support			
6.1 Specialist centres and local care teams should offer information and refer patients and their families to services that can assist patients with financial planning and support (including family/caregiver relief, disability benefits, caregiver allowances if available, etc). This could be done in partnership/ consultation with national and/or local patient organisations.	87.7% (45.3%)	20.9% (40.7%)	N/A
6.2 Specialist centres and local care teams should offer information on the hereditary nature of ATTRv amyloidosis to support patients when informing family members on their diagnosis. This could be done in partnership/ consultation with national and/or local patient organisations.	93.4% (65.1%)	50.0% (31.4%)	N/A
7.0 Spiritual support and social networking			
7.1 Specialist centres and local care teams should reinforce the value of, and provide information about, patient advocacy organisations, support groups and social media channels, and how these organisations can help as a means of exchanging experiences, forming connections and finding support and education.	89.6% (51.9%)	30.2% (41.9%)	N/A
7.2 Where specific advocacy groups/patient organisations do not exist, healthcare teams should consider facilitating introductions between patients and family members, with their consent.	76.4% (34.0%)	16.5% (37.7%)	N/A
7.3 Specialist centres and local care teams should consider extending palliative care services to patients with life-limiting amyloidosis.	91.4% (56.7%)	26.7% (39.5%)	N/A

Application in practice as a core part of care: High: ≥66% of HCPs. Moderate: ≥50%–<66%. Low: ≥25%–<50% of HCPs. Very low: 25% of HCPs.
*Defined as 'strongly agree' and 'agree' responses.
ATTRv, hereditary transthyretin-mediated amyloidosis; EQ-5D, EuroQol 5-Dimension; GI, gastrointestinal; HCP, healthcare professional; N/A, not available.

Evaluating each recommendation, there was a significantly higher level of agreement based on weighted averages of responses among HCPs than among PAG representatives (p<0.0005 Mann-Whitney U test using Bonferroni correction for multiple testing) on: the importance of timely and regular MDT monitoring of asymptomatic gene carriers (recommendation 1.7), mandatory genetic testing at diagnosis (recommendation 1.1), MDT baseline assessment after diagnosis (recommendation 1.4); tailored follow-up for each patient according to their signs and symptoms and expected disease course (recommendation 2.1); minimum follow-up interval of 6–9 months (adjusted according the patients' disease course) (recommendation 2.7) and finally, the need for joint treatment decisions based on the evidence, and discussion with MDT and patient (recommendation 1.5).

Online supplemental table S1 outlines the top 12 recommendations where there was greatest agreement based on weighted averages of responses. The highest level of agreement among PAG representatives was for: the regular referral and assessment by a nutritionist (recommendation 3.5.1), patient education (recommendation 1.14) and information for families (recommendation 6.2), the role of specialist centres in providing information on national PAGs (recommendation 7.1), informed treatment decisions (recommendation 1.5); the need for interim review (telemedicine) between scheduled visits with worsening of symptoms (recommendation 2.8) and the need for training of HCPs to increase awareness of the disease (recommendation 1.1). By contrast, the highest level of consensus among HCPs was related to the recommendations on: informed treatment decisions

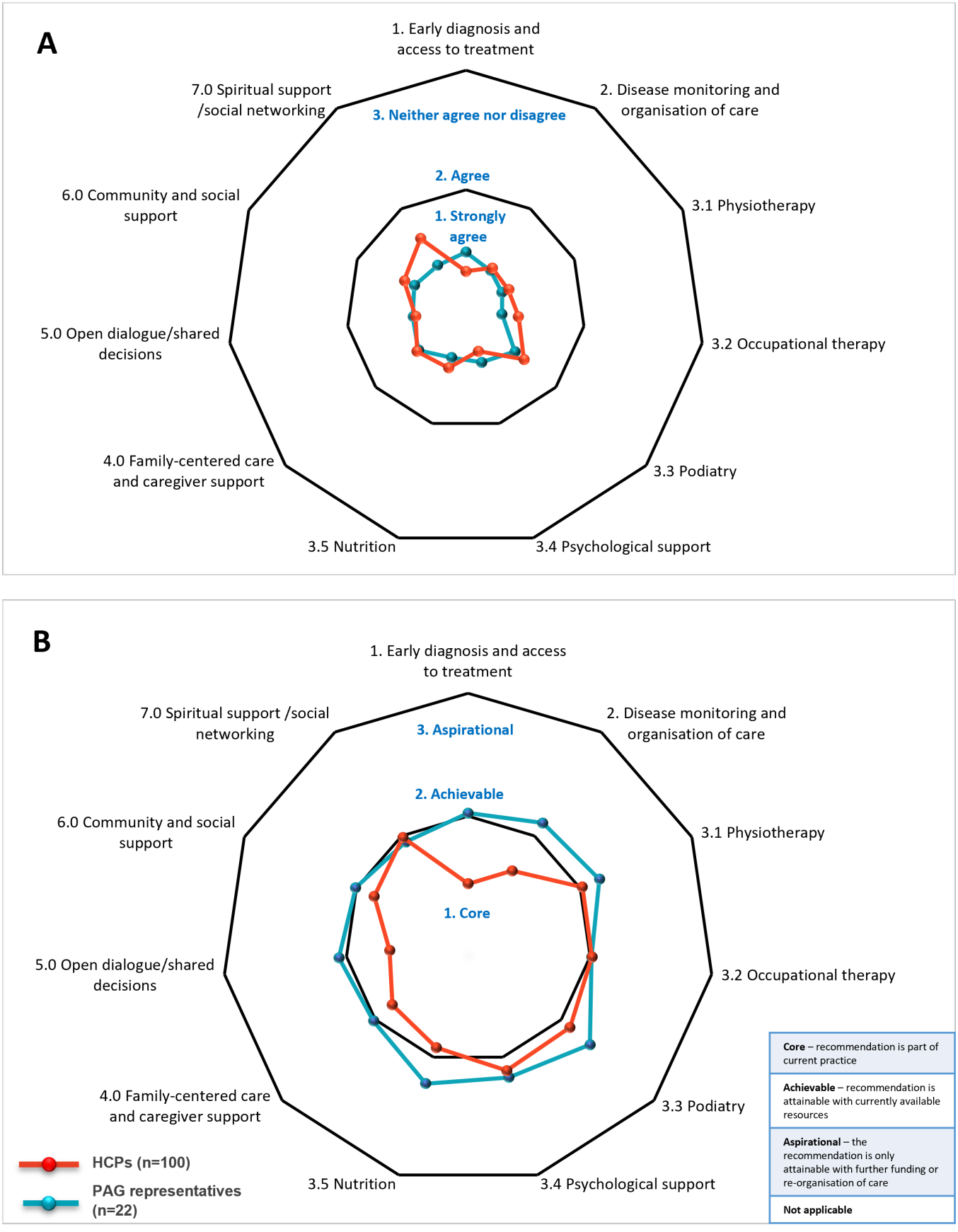

Figure 4 Votes from PAG representatives and HCPs on (A) level of agreement and (B) application in practice for recommendations grouped by core themes (based on weighted averages from all responders; n=122). HCP, healthcare professional; PAG, patient advocacy group.

(recommendation 1.5), follow-up genetic counselling after diagnosis (recommendation 1.3), care at specialist centres (recommendation 2.3); monitoring asymptomatic patients (recommendation 1.7), patient education following diagnosis (recommendation 1.8) and independent living aids (recommendation 3.1.4).

DISCUSSION

This research highlights the challenges associated with the holistic care of patients, particularly in rare diseases, and recognises the crucial contribution of PAGs in representing the experiences of people affected by these diseases. By working in consultation with PAGs on the Primary Panel, this Delphi survey established a clear consensus with PAGs and the wider clinical community on the recommendations for holistic care of patients with ATTRv amyloidosis. However, differing experiences across specialist centres meant that the level of implementation of the recommendations in practice was relatively low compared with level of consensus. In this respect, the written feedback from the international voting panel provides additional insights, as we discuss below.

Early diagnosis and access to treatment

ATTRv amyloidosis is a progressive disease, which is now treatable if diagnosed in its early stages.[37] There was broad consensus from the international voting panel that genetic testing should be mandatory to confirm the diagnosis in symptomatic patients with ATTR amyloidosis (recommendation 1.1), and that access to follow-up genetic counselling should also be provided for all patients and their families (recommendation 1.3).[22 35] Voters observed that diagnosis of symptomatic disease may also be supported by the detection of amyloid in the tissue.[22 38–40]

When considering the current level of access to diagnostic genetic testing, most HCP voters (69.4%) reported that this was part of standard care within their institutions (recommendation 1.1), although respondents commented that the responsibility for requesting a genetic test (often by neurologists, cardiologists, internists or geneticists) will differ depending on the clinician's experience and local practice. An additional practical consideration are the resources (and training of members of MDT) which would be required for the implementation of mandatory pretest counselling and informed consent from patients before genetic testing.

Definitive characterisation of the amyloid type using immunohistochemistry or mass spectrometry is a prerequisite for effective therapy (recommendation 1.2); however, less than half of the HCP voting panel considered this to be a core part of current care, while almost one-third of HCPs commented that this is achievable with available resources. Although mass spectrometry is now considered the gold standard for amyloid typing,[41 42] the availability of tests will depend on local resources, and tissue samples may need to be sent to specialised laboratories if in-house facilities are not available.

Family follow-up and cascade genetic testing

The international voting panel also agreed on the need for genetic counselling for patients as well as their families to support presymptomatic genetic testing in at-risk relatives and advice on prenatal testing (recommendation 1.3). Two-thirds (67.0%) of HCPs viewed genetic counselling as a core activity in everyday practice, although fewer HCPs (57.7%) considered that cascade genetic testing was part of core care (recommendation 4.1). Commenting on these recommendations, voters noted that presymptomatic genetic testing of at-risk family members younger than 18 years is not recommended (and may be prohibited in some countries). Except for a few very early-onset TTR variants, genetic counsellors should advise individuals that not all gene carriers will develop the disease, and that penetrance is highly variable and symptom onset tends to occur in later life.[43] Prenatal and preimplantation testing (recommendation 1.3) may depend on local regulations, but it was the view of some respondents that genetic counselling on reproductive options should be offered to all couples on request, to allow decisions to be made according to individual country-level practice and personal choice.

More than 90% of voters endorsed the timely multidisciplinary baseline assessment of symptomatic patients after diagnosis to guide treatment decisions (recommendation 1.4) as well as the monitoring of asymptomatic gene carriers (recommendation 1.7) to identify and treat the first signs of disease. As published elsewhere, the frequency of assessment of asymptomatic gene carriers should be guided by the age, genotype and expected phenotype for each individual.[22 34 35]

Initiating disease-modifying treatment

Without exception, all voters agreed that treatment decisions should be informed by the latest evidence and made jointly with patients (recommendation 1.5); although, it was noted that treatment access also informs treatment choice. Notably, while 91.7% of all voters agreed (including 75.8% who strongly agreed) with the recommendation to initiate treatment immediately after diagnosis (recommendation 1.6), only 66.3% of HCPs indicated that this was a core part of current care. If disease-modifying drugs are not available, first-line treatment may include liver transplantation in a limited number of eligible patients depending on genotype, phenotype and patients' general health.[20]

Patient education

Voting panel members observed that it is the joint role of patient associations and specialist centres to ensure that patients and their support networks are provided with adequate information (recommendation 1.8). However, only half of HCPs considered education to be a core part of present-day practice. We hope that this guidance

will encourage more clinicians to recommend national/regional patient organisations to their patients as a good starting point in support of this goal. Given the rapid evolution of treatments for this condition, voters also commented that both patients and clinicians would also benefit from knowing how to access information on, and participate in, clinical research studies.

Disease monitoring and organisation of care

The recommendation for the coordinated multidisciplinary follow-up of patients (recommendation 2.4) was based largely on published expert guidance[34] and received a high level of endorsement (82.1%). Over half (58.5%) of HCPs confirmed that consistent follow-up of the patients at the same centre was the current core practice (recommendation 2.6), and 61.3% of HCPs endorsed a minimum follow-up interval of 6–9 months, adjusted based on the patient's evolving symptoms and treatment (recommendation 2.7). The role of internists as part of the multidisciplinary support team should also be acknowledged (recommendation 2.4).

There was, however, a divergence of opinion among HCPs on the feasibility of implementing coordinated access to allied HCPs via local/regional centres and primary care. Largely, the availability of local support (near the patient's home) to assist long-term care (recommendation 2.11), assistance from specialist centres to facilitate and coordinate access to other specialist services (recommendation 2.10), care coordinators (recommendation 2.12), HCP disease state education and training (recommendation 2.13), or the evolution of local or regional services beyond tertiary specialist centres (recommendation 3.0) were not considered a core part of current practice by the majority (>67%) of HCP respondents. Although, between 33% and 44% of HCPs voted that each of these recommendations could be achievable with currently available resources.

Of note, 95.7% of voters observed that the unpredictable disease course (even for some patients within the same family) may require the implementation of an individual care plan (recommendation 2.1). Only one-third of HCP voters regarded telemedicine/online review with patients (if in-person review is not possible) as a core part of current care (recommendation 2.8), although a further 41.3% considered that this was potentially achievable with available resources.

Maintenance of physical and mental health

In developing the recommendations, the Primary Consensus Panel considered that there is limited psychological support for patients with ATTRv amyloidosis, either due to insufficient funding and/or lack of multidisciplinary working. Furthermore, vision and nutrition are often overlooked as key systems impacted by the disease, requiring monitoring and healthcare input.

Physical rehabilitation

Most international voters agreed on the recommendations relating to physical rehabilitation including physiotherapy (3.1.1–3.1.4; 89.1%–97.2%), occupational therapy (3.2.1–3.2.3; 91.7%–99.1%), podiatry (3.3.1–3.3.2; 83.2%–84.1%) as well as psychological support (3.4.1–3.4.3; 92.5%–98.1%) and nutrition (3.5.1–3.5.4; 80.2%–94.3%); although, application of the these recommendation is practice was low according to voting HCPs.

Psychological support

Notably, despite strong agreement among more than 90% of voters on the recommendations for psychological support (recommendations 3.4.1–3.4.3), core services to support the psychological assessment and support for patients, family members and caregivers during 'moments of crisis' were only currently available and practiced in up to 25% of clinics (according to voting HCPs). Written feedback from voters (both HCPs and PAG representatives) emphasised the optional nature of psychological support, while recognising the ongoing stigma around mental health services and mental health needs. These findings suggest that there is still much work to be done in acknowledging that the psychological needs of patients are equal to their physical needs and that there should be no stigma in needing or wanting support in these areas.[27 28 44] HCPs may also need training to be able to support their patients to overcome the discomforts associated with mental health issues.

Nutrition

Perhaps least controversial was recommendation 3.5.1 on identifying and referring patients with gastrointestinal symptoms to a nutritionist (75.5% of all voters strongly agreed), with 52.3% of HCPs indicating that core services were already in place. As identified when writing the recommendations, the European Society for Clinical Nutrition and Metabolism strongly recommends the combined use of physical diagnostic criteria and nutritional screening to identify the degree of malnutrition or cachexia in patients, despite a 'very low' level of available evidence for these tools.[45] The guidance in medical literature emphasises prevention (through the early identification of at-risk patients) (recommendation 3.5.2).[45] Whenever possible, the Primary Consensus Panel recommended that collaboration between expert nutritionists and physical therapists should be encouraged, to help patients maintain muscle strength, physical functioning and metabolic activity (recommendation 3.5.3); these later goals were widely endorsed by voters.

Family-centred care and caregiver support

The evidence from published focus groups and patient surveys shows that patients with ATTRv amyloidosis are not only affected by the physical consequences of their illness, but also by its effects on their families.[23] At the time of diagnosis, many patients have concerns about the impact on their children, grandchildren and siblings who

may have also inherited the genetic variant. Despite such challenges, family members are identified as 'important champions for providing motivation, inspiration and support'.[23] In writing these guidelines, the PAG representatives advocated for the involvement of family members and caregivers in discussions with the healthcare team on the requirements for home support and rehabilitation (recommendations 4.2–4.3). In addition, the recommendations suggest that cascade genetic testing should be offered to families after genetic counselling (see discussion on recommendation 4.1 above). In response to this suggested guidance, several respondents to the survey observed that discussions with family members and caregivers should be voluntary, and only with the index patient's agreement; HCPs need to be sensitive to the needs of families who may be already struggling to cope with psychological distress and guilt associated with diagnosis.

Patient–HCP dialogue and shared decision-making

Recommendations were also developed with PAG representatives to encourage open communication and shared decisions as part of the core care, to honour patient autonomy and respect patients who may also be 'experts in the room', especially regarding their genotype and evolving symptoms (recommendations 5.1–5.3).[3 15] As observed by Budych *et al* there is evidence that 'patients with rare diseases often learn to fulfil their role as experts in the treatment process'.[3 15] Recommendation 5.1 on open discussion with patients and their families regarding the hereditary nature of the disease and the likely course of the disease, gained one of the higher levels of endorsement compared with other recommendations (65.7% 'strongly agree' among all voters) and application in current practice (54.7% among HCPs). Stewart *et al*[3] observed that an important goal for care is helping patients maintain their autonomy, and that therapies for ATTRv amyloidosis, which have moved beyond symptomatic management to modification of disease progression, may help ultimately reduce the disease burden and patients' reliance on caregivers.[3] Some respondents observed that when discussing patients' and caregivers' short-term and long-term priorities (recommendation 5.2) and the course of disease (recommendation 5.1), care should be taken to avoid predicting the outcomes following treatment and the likely disease course for this highly heterogeneous disease.

Access to community and social support, social networking and spiritual support

Beyond medical support, the panel considered the joint role of specialist centres and local care teams in helping patients and families access financial planning and social support services (recommendations 6.1–6.2), which achieved a high level of consensus (87.7% of all voters) but a low level of application in practice (20.9% of HCPs). This support for patients could be achieved through partnership/consultation with national and/or local patient organisations, who are often better suited than HCPs in helping families navigate financial issues (pensions, mortgages, insurance) and benefits claims.

Finally, it is important to acknowledge the value of patient support groups, online or in-person forums, and social media networking as a means of connecting people who are living with ATTRv amyloidosis (recommendation 7.2), which was endorsed by 76.4% of the voting panel. The authors would like to acknowledge the contribution of a range of community programmes for patients and families to help aid acceptance, build resilience and support well-being, including clinical (psychological), social (networking) and spiritual support. Notably, more than 90% of voters agreed with extending palliative care services to patients with life-limiting amyloidosis (recommendation 7.3); however, once again only 26.7% of HCPs identified this recommendation as core to their current practice.

Strengths and limitations

The Delphi study included PAG representatives, expert physicians and allied HCPs across various specialisms, to ensure the recommendations were patient-centred and designed around their complex multidisciplinary care needs. A large panel of voters was recruited and response rates were similar across PAG representatives and HCP experts. Consensus was sought on 50 draft recommendations encompassing a broad range of themes. Furthermore, experts were invited from 27 countries across diverse geographic regions, which provided a benchmark assessment on the current application in practice of each recommendation. The survey was translated into French, Spanish and Japanese to facilitate understanding, and also invited anonymised written feedback from patient representatives and HCPs with a special interest in this rare disease, to broaden responses. Although the Delphi survey succeeded in recruiting a large panel of international voters, regional differences in opinion and practice were not analysed.

While a large panel of international voters was recruited, the majority of invited experts were European, which may impact how representative the recommendations are outside of this region. Additionally, country-level data were not explored here, so recommendations do not capture differences across countries' healthcare systems and payers. HCPs from a broad range of specialisms were recruited; however, the majority were from specialist centres with limited participants from referral centres. Additionally, the results of a Delphi consensus are highly dependent on the interpretation of statements. The impact of any misinterpretation has been minimised through translation and independent review by the primary consensus panel, and HCP and PAG representatives were identified based on their respective expertise and familiarity with the topic.

CONCLUSIONS

We believe that these are the first published recommendations to recognise the value of representatives from the

patient community in advocating for the clinical, social and spiritual needs of people affected by ATTRv amyloidosis. We hope that this study will encourage further discussion and guidance on how to develop services to address the complex needs of those affected by this rare disease.

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Acknowledgements The Primary Consensus Panel would like to thank all patient association representatives and healthcare professionals who took part in this survey, including representatives from the following institutions who agreed to be named: Argentina: Instituto de Neurociencias Buenos Aires; Hospital Británico, Buenos Aires; Raúl Carrea Institute for Neurological Research, FLENI, Buenos Aires; Australia: St Vincent's Multidisciplinary Amyloidosis Centre, Darlinghurst, NSW; Westmead Amyloidosis Centre, Westmead, NSW; Eastern Health, Melbourne; Austria: Division of Cardiology and Emergency Medicine, Favoriten Clinic, Vienna; Belgium: Ghent University Hospital, Neuromuscular Reference Center, Ghent; Hôpital Erasme, Université Libre de Bruxelles; Bolivia: Clínica Foianini, Santa Cruz de la Sierra; Brazil: Referral Service for Rare Diseases of Pernambuco; Hospital das Clínicas, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo; CEPARM, Amyloidosis Center, University Hospital, Federal University of Rio de Janeiro; Amyloidosis Center of Niterói Hospitalar Complex-DASA, Rio de Janeiro; Canada: AmyloCHUM, Amyloidosis Program, Centre Hospitalier de l'Université de Montréal, Montréal; London Health Sciences Centre, University Hospital, London, Ontario; France: CHU Limoges; Henri Mondor University Hospital-APHP Paris Est, Créteil; Competence Center for Cardiac Amyloidosis, Cardiology Department, Bichat-Claude Bernard Hospital and Université de Paris Cité, Paris; French National Reference Center for Hereditary ATTR Amyloidosis, Hôpital Bicêtre-AP-HP, Université de Paris-Saclay, Paris; Electroneuromyography and Neuromuscular Department, Pierre Wertheimer Hospital, Hospices Civils de Lyon; Germany: Interdisciplinary Amyloidosis Center of Nord Bavaria, University Hospital of Wuerzburg; Amyloidosis Center Charité Berlin; Italy: Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan; Unit of Neurology, AOU Policlinico 'G. Martino', Messina; Japan: Shinshu University School of Medicine, Matsumoto, Nagano Prefecture; Nagoya University Graduate School of Medicine, Nagoya; Republic of Ireland: Tallaght University Hospital, Trinity College Dublin; Spain: Multidisciplinary Amyloidosis Unit, Juan Ramón Jiménez University Hospital, Huelva; Hospital Clinico San Carlos, Madrid; Hospital Universitario Son Llàtzer, Palma de Mallorca; Amyloidosis, Instituto de Investigación Sanitaria de las Islas Baleares (IdISBa), Palma; Sweden: Amyloidosis Center, Umeå University Hospital, Umeå; Taiwan: Cardiovascular Medical Center, Far Eastern Memorial Hospital, New Taipei City; The National Yang Ming Chiao Tung University, School of Medicine, Taipei; The Netherlands: Groningen Amyloidosis Center of Expertise, University Medical Center Groningen; United Kingdom: National Amyloidosis Centre, UCL & Royal Free Hospital, London; Wiltshire Health and Care; Liverpool Heart and Chest Hospital; St George's Hospital, London; United States of America: University of Louisville School of Medicine, Rudd Heart & Lung Center, Louisville, Kentucky; Boston University.Representatives from the following patient associations agreed to be acknowledged: Argentina: Alianza Argentina de Pacientes (ALAPA); Brazil: Associação Brasileira de Paramiloidose (ABPAR); Canada: Canadian Amyloidosis Support Network (CASN); TTR Amyloidosis Canada; Ireland: Amyloidosis Ireland; New Zealand: New Zealand Amyloidosis Patients Association (NZAPA); The Netherlands: Stichting Amyloïdose Nederland (SAN); Spain: Asociación Balear de la Enfermedad de Andrade; Sweden: Famy Norrbotten; United Kingdom: European Alliance for Patient Access (EAfPA); Cardiomyopathy UK; UK ATTR Amyloidosis Patients' Association (UKATPA); United States of America: Alliance for Patient Access (AfPA); Amyloidosis Research Consortium (ARC); Amyloidosis Support Groups (ASG); Mackenzie's Mission and the Amyloidosis Speaker's Bureau; Amyloidosis Foundation.

Contributors LO was involved in developing the study design, writing the manuscript, interpretation and analysis of data, and has and approved the final version of the manuscript. RC was involved in developing the study design, writing the manuscript, interpretation and analysis of data, and has and approved the final version of the manuscript. JA was involved in developing the study design, writing the manuscript, interpretation and analysis of data, and has and approved the final version of the manuscript. CB was involved in developing the study design, writing the manuscript, interpretation and analysis of data, and has and approved the final version of the manuscript. TB was involved in developing the study design, writing the manuscript, interpretation and analysis of data, and has and approved the final version of the manuscript. IC was involved in developing the study design, writing the manuscript, interpretation and analysis of data, and has and approved the final version of the manuscript. FD was involved in developing the study design, writing the manuscript, interpretation and analysis of data, and has and approved the final version of the manuscript. AF was involved in developing the study design, writing the manuscript, interpretation and analysis of data, and has and approved the final version of the manuscript. FK was involved in developing the study design, writing the manuscript, interpretation and analysis of data, and has and approved the final version of the manuscript. TL was involved in developing the study design, writing the manuscript, interpretation and analysis of data, and has and approved the final version of the manuscript. L-OL was involved in developing the study design, writing the manuscript, interpretation and analysis of data, and has and approved the final version of the manuscript. AM was involved in developing the study design, writing the manuscript, interpretation and analysis of data, and has and approved the final version of the manuscript. VN was involved in developing the study design, writing the manuscript, interpretation and analysis of data, and has and approved the final version of the manuscript. TC was involved in developing the study design, writing the manuscript, interpretation and analysis of data, and has and approved the final version of the manuscript. TL is study guarantor.

Funding This study, and its resultant presentations and publications, were funded by Alnylam Pharmaceuticals. Medical writing support was provided by Rae Hobbs of Lumanity, funded by Alnylam Pharmaceuticals.

Competing interests LO has received speaker honoraria from Pfizer, Akcea and Alnylam; and has received honoraria for participation on advisory panels from Alnylam, Sobi, AstraZeneca, Novo Nordisk, and Pfizer. RC has received honoraria for participation in webinars from Alnylam; has received honoraria for participation in symposia from Alnylam; and has received honoraria for participation on an advisory panel from Alnylam. JA has received honoraria for participation on an advisory panel from Alnylam. CB has received honoraria for participating in symposia from Alnylam; and has received honoraria for participation on an advisory panel from Alnylam. TB received honoraria for participation in webinars from Alnylam; and has received honoraria for participation on an advisory panel from Alnylam. IC has received research funding from Pfizer; has received honoraria for participation in advisory boards from Pfizer, Alnylam, and Akcea; and has received financial support as primary investigator from Alnylam, and Ionis. AF has received honoraria for participation on an advisory panel from Alnylam. FK has received honoraria for participation in educational presentations from Alnylam; and has received honoraria for participation on an advisory panel from Alnylam. TL is an employee and stockholder of Alnylam Pharmaceuticals. L-OL received honoraria for participation on an advisory panel from Alnylam. AM has received honoraria for participation in webinars from Alnylam; and has received honoraria for participation on an advisory panel from Alnylam. VN has received honoraria for participation on an advisory panel from Alnylam. TC has received speaker honoraria from Pfizer, Alnylam, GlaxoSmithKline, Prothena and Akcea; has received expenses support for scientific meetings from Pfizer, Alnylam, Ionis, and Biogen; and has received honoraria for participation on an advisory panel from Alnylam. FD has no competing interests to declare.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval Formal ethical approval was not required for this study in accordance with UK Health Research Authority research criteria. All participants gave informed consent prior to taking part in the study.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

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