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Review Article

# The patient pathway in ATTR-CM in Greece and how to improve it: A multidisciplinary perspective

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ABSTRACT

Transthyretin amyloid cardiomyopathy (ATTR-CM) is an underdiagnosed disease associated with high mortality rates and the patient journey is characterized by increased complexities. Accurate and timely diagnosis and prompt initiation of disease-modifying treatment constitute the contemporary unmet need in ATTR-CM. ATTR-CM diagnosis is characterized by considerable delays and high rates of misdiagnosis. The majority of patients present themselves to primary care physicians, internists, and cardiologists, and many have undergone repeated medical evaluations before an accurate diagnosis has been made. The disease is diagnosed mainly after the development of heart failure symptoms, reflecting a long course of missed opportunities before diagnosis and disease-modifying treatment initiation. Early referral to experienced centers ensures prompt diagnosis and therapy. Early diagnosis, better care coordination, acceleration of digital transformation and reference networks, encouragement of patient engagement, and implementation of rare disease registries are the key pillars to improve the ATTR-CM patient pathway and achieve important benefits in ATTR-CM outcomes.


## 1. Introduction

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressively debilitating rare condition associated with high mortality.[1] It is caused by instability of transthyretin (TTR) protein, the formation of amyloid deposits in the extracellular space of the myocardium, and, subsequently, infiltrative cardiomyopathy.[2-4] ATTR-CM is categorized into two predominant subtypes: hereditary (variant) ATTR-CM (hATTR-CM) and wild-type ATTR-CM (wtATTR-CM). Hereditary ATTR-CM is inherited in an autosomal dominant pattern. In wtATTR-CM, which is associated with aging,[5] TTR is not mutated but misfolded.[6] Although a complete understanding of the pathogenesis of ATTR-CM is evolving, cardiac toxicity is believed to occur due to the starvation of cells by extracellular amyloid deposits and direct toxicity from the attachment of amyloidogenic TTR to the cell membranes, disruption of calcium ion levels, inflammation and cell death.[7-9]

ATTR-CM has been considered a rare disease. Contemporary data suggest that the diagnosis of ATTR-CM is commonly missed among diagnoses with similar phenotypes, such as aortic stenosis[10] and heart failure with preserved ejection fraction (HFpEF),[11] leading to significant delays in proper disease management and treatment. Prevalence rates for cardiac amyloidosis (CA) vary according to the clinical phenotype and the applied screening modality. A

*Abbreviations:* AL, amyloid light chain; ATTR-CM, transthyretin amyloid cardiomyopathy; CTS, carpal tunnel syndrome; FLC, free light chain; hATTR-CM, hereditary transthyretin amyloid cardiomyopathy; HCM, hypertrophic cardiomyopathy; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HRQOL, heart-related quality of life; ICD, implantable cardiac defibrillator; LVH, left ventricular hypertrophy; NAC, National Amyloidosis Centre; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association; SF12, short form 12 health survey; SPECT, single photon emission computed tomography; SPIE, serum protein electrophoresis with immunofixation; THAOS, Transthyretin Amyloidosis Outcomes Survey; TRACS, Transthyretin Amyloidosis Cardiac Study; TTR, transthyretin; UPIE, urine protein electrophoresis with immunofixation; Val122Ile, valine 20 to isoleucine mutation; wtATTR-CM, wild-type transthyretin amyloid cardiomyopathy.

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recent systematic review of clinical studies has revealed the magnitude of the problem, with CA prevalence rates reaching 14.7% in patients with hypertrophic cardiomyopathy (HCM) phenotype (n = 1,697), 15% in patients with heart failure (HF) and left ventricular hypertrophy (LVH) (n = 86), 28.2% in patients with HFpEF of unknown cause assessed with biopsy (n = 259), and 15.9% in patients with severe aortic stenosis (n = 151).[12] Another systematic review of screening studies reported higher than previously thought mean prevalence rates of 7% for patients undergoing surgery for carpal tunnel syndrome (CTS), 2% for patients with conduction disorders, 7% for HCM, 8% for aortic stenosis, 12% for HFpEF, 10% for heart failure with reduced or mildly reduced ejection fraction.[13]

The emergence of disease-modifying therapy for ATTR-CM, which improves mortality, need for hospitalization, and quality of life (QOL),[14] has redefined the unmet need for this population to improve diagnosis, in both timing and accuracy. The objective of this study is to identify and lay out the complexities of ATTR-CM disease management, provide an expert perspective regarding the Greek healthcare setting, and outline practical recommendations on how to improve the patient journey, based on international clinical guidelines and best practices for healthcare quality improvement.

## 2. ATTR-challenges in disease management

### 2.1. Disease course, prognosis, and associated burden

ATTR-CM is a disease that evolves slowly, with patients usually being diagnosed at advanced stages.[15-17] The age of onset depends on various factors, such as genotype, gender, and region; however, ATTR-CM is typically a disease of advanced age,[2,18-20] with wtATTR-CM predominantly affecting men >60 years of age.[21-23] ATTR-CM is associated with multi-organ complications.[3,10,23-25] Cardiac involvement plays a pivotal role, especially in wtATTR-CM. The heart is a predominant target for amyloid deposits.[15,26,27] As infiltration advances, hypertrophy, conduction disorders, and diastolic and systolic dysfunction develop, leading to symptoms and signs of HFpEF due to restrictive physiology.[24,28] Patients may exhibit dyspnea, fatigue, reduced functional reserve, edema, and overall reduction in quality of life (QOL).[29,30] Other “red flags” for suspecting ATTR-CM include increased biomarker levels, particularly troponin, and N-terminal prohormone of brain natriuretic peptide (NT-proBNP), that are disproportionate to the clinical context; hypertension that resolves and requires de-escalation of treatment; and intolerance to common antihypertensive and HF medications, such as angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), and beta-blockers.[29] Syncope or presyncope is frequent; it is caused by conduction system disorders, which frequently require pacemaker implantation, while postural hypotension and dysautonomia may coexist.[31] Atrial fibrillation is more common in wtATTR, and recent data from a multi-centre study have shown higher rates of conduction disorders and pacemaker implantation in patients with wtATTR.[23] Patients with ATTR-CM may also suffer from aortic stenosis.[5,23] This wide range of cardiac symptoms and signs, which are also present in common cardiovascular conditions, often lead to missed and/or delayed diagnosis and a negative impact on survival, as physicians may treat the obvious conditions but may not provide a thorough etiological diagnosis that either excludes or confirms ATTR-CM. This challenge is further exacerbated by data showing that the benefit of treatment of ATTR-CM patients with conventional HF therapies, such as ACEi and beta-blockers, is not well established and sometimes may be harmful.[32]

ATTR-CM is also characterized by non-cardiac symptoms due to soft tissue, neurologic, gastrointestinal, and eye involvement.[19,24,29,33,34] The earliest extracardiac sign of ATTR-CM is often CTS, found in up to 55% of individuals with wtATTR-CM, occurring approximately 5-7 years before diagnosis.[21,35,36] In wtATTR, patients may report bilateral CTS many years before the cardiomyopathy diagnosis.[3,24,37] Other ligaments and tendons may be affected, presenting as biceps tendon rupture or spinal stenosis.[5,23] A study of 111 patients with wtATTR-CM showed that 33% of patients had ruptured distal biceps tendons versus 3% of controls.[38] ATTR-CM has also been associated with an increased rate of hip and knee arthroplasty.[39] Patients may exhibit peripheral neuropathy and autonomic dysfunction.[3,23,24,29] They frequently report gastrointestinal symptoms, which may result in weight loss.[3] Intravitreal amyloid depositions may cause ophthalmological manifestations, whereas scalloped pupils are specific to ocular involvement.[3,23,25]

There are three prognostic systems for patients with ATTR-CM derived from series in the Mayo Clinic,[22] the National Amyloidosis Centre (NAC),[40] and Columbia University.[41] The NAC system utilizes estimated glomerular filtration rate (eGFR) and NT-proBNP as staging variables, with the poorest outcomes for patients with eGFR <45 mL/min and NT-proBNP >3,000 pg/mL. It has been shown to predict survival across the disease trajectory of ATTR-CM[42] and is recommended as a monitoring tool in the European consensus document.[4] The Mayo Clinic system uses NT-proBNP >3,000 pg/mL and troponin-T >0.05 ng/mL as cut-offs for advanced disease, whereas the Columbia system is based on daily furosemide dose and New York Heart Association class.

Mortality in ATTR-CM is driven mainly by HF and arrhythmias.[5,10,24,28] In the prospective Transthyretin Amyloidosis Cardiac Study (TRACS), HF, sudden death, and sepsis were the most frequent mortality causes,[1] and a French retrospective study (220 patients with hATTR, 158 patients with wtATTR, and 187 patients with amyloid light chain [AL] amyloidosis) found that mortality was primarily due to worsening HF and sudden death, whereas infection was the main non-cardiac cause.[43] Untreated wtATTR-CM is associated with a median survival of 32-43 months after diagnosis, suggesting a considerable survival gap due to delayed diagnosis.[1,21,33] A recent meta-analysis of data on ATTR survival (n = 17,340), which did not include patients receiving new therapeutic agents, showed that wtATTR survival rates are as low as 91.9% (95% CI 90.7-93.2) at 1 year, 76% (95% CI 73.0-78.9) at 2 years, and 48% (95% CI 40.9-55.1) at 5 years. These rates are slightly higher than age-adjusted hATTR survival at 1 and 2 years.[12] Recent data have also shown that CA is associated with a poorer prognosis than dilated or HCM and hypertensive, ischemic, or valvular heart disease.[44]

Data about the ATTR-CM disease burden are scarce; however, it has been described as having an overwhelming impact on patients, families, and caregivers.[45] Patients typically report physical and social deterioration, and poor heart-related quality of life (HRQOL) scores, particularly affecting wtATTR and valine 20 to isoleucine mutation patients.[46] HF, the chief manifestation of ATTR-CM disease progression, causes symptoms that substantially impair patients’ QOL. Poor HRQOL is common, deteriorates along with disease progression, and is associated with increased mortality risk, irrespective of HF severity.[24,28,45]

The burden associated with ATTR-CM expands to substantial economic costs and significant utilization of healthcare resources. A recent study of 1,831 patients with ATTR-CM and 1,831 patients with HF without ATTR-CM showed that ATTR-CM is characterized by double outpatient specialist evaluations and 50% more hospitalizations in the first year after diagnosis, compared with HF without ATTR-CM.[2-4,47] Patients have reported visits to multiple physicians before being correctly diagnosed, with cardiologists frequently failing to identify the disease.[1,17,19,48,49] Caregivers also experience significant burden, and poor scores have been reported

on the short form 12 health survey physical and mental health components. They have also reported work impairment and a high amount of time spent providing care to patients (mean 45.9 h/wk). Work productivity was impacted for employed patients and caregivers. The level of burden reported among the US caregivers was comparable with the levels reported by caregivers of patients suffering from Alzheimer's disease in the United States (ZBI score 34.3 ± 16.7 vs 30.6).[50]

The timely initiation of disease-modifying treatment is a hallmark in ATTR-CM treatment because it can substantially improve the disease course by slowing disease progression, decreasing hospitalization rates, and improving mortality rates and QOL.[14] When HF develops, disease-modifying treatment should be administered on top of conventional HF treatment; however, the benefit of conventional HF therapies like ACEi, ARB, and beta-blockers is not well established in ATTR-CM,[32,51] and they are often not well tolerated due to hypotension and conduction disorders. The common presence of multimorbidity, polypharmacy, and frailty increase management complexity.[52] These facts underline the need for timely diagnosis to achieve earlier disease modification and maximize patient and societal benefit.

### 2.2. Diagnostic challenges and delays

ATTR-CM is characterized by substantial rates of misdiagnosis that have been described to reach 34-57%.[29,53] Physician-related factors include inconsistent knowledge across medical specialists, shortage of dedicated, experienced centers, misconceptions about diagnosis, use of diagnostic tests with insufficient specificity, and a false conception that ATTR-CM is untreatable.[53] The substantial genotypic and phenotypic heterogeneity of ATTR-CM and its systemic nature are the most important disease-related factors that make diagnosis a challenging task, along with the need for histological confirmation in specific cases and the assumed rarity[17,25] (Table 1). This may especially be the case for patients with little or no neurologic involvement.[25] Cardiac symptoms are non-specific, and they mimic other disorders, e.g., HFpEF, hypertensive cardiomyopathy, and conduction disorders, which are common in this age group. In addition to the age-dependent nature of ATTR-CM, many patients present with comorbidities and frailty, which overlap with the presenting phenotype. Typically, a patient's condition undergoes a long, unrecognized evolution, and diagnosis usually happens after the development of serious cardiac symptoms.[19] ATTR amyloidosis may also be commonly confused with AL amyloidosis.[17,48] Both AL amyloidosis and ATTR amyloidosis have a heterogeneous presentation that can include cardiac involvement, making differential diagnosis challenging.[24,53]

Due to these difficulties, there is a significant delay between symptom onset and diagnosis, with patients commonly reporting delays of more than 4 years.[17] A literature review of 23 studies reported weighted means of mean diagnostic delays at 6.1 years for wtATTR-CM.[54] Another study from the Yale Cardiomyopathy Program (N = 34) reported median times to diagnosis of 922 to 90 days from the first to fourth clinical manifestation, respectively, suggesting a significant delay.[19] They reported time from disease onset to diagnosis to range from a median of 4.3 years in patients with CTS manifestation to 4 months earlier in patients with LVH. They also reported that patients had an average of 4.4 ± 2 amyloid-related clinical manifestations upon diagnosis. The median time (days) to diagnosis for common clinical manifestations was the longest for CTS (1,616), 960 for peripheral neuropathy, 469 for the first episode of dyspnea, and 465 for pacemaker or implantable cardioverter defibrillator implantation.[19] Another THAOS study (N = 421) reported delayed diagnosis (mean 6.4 years) in both wtATTR-CM and hATTR-CM patients.[55] The THAOS registry reported wtATTR-CM patients to have a mean age of 74.4 years at the time of diagnosis, with disease onset estimated at 6.4 years earlier.[56] Similarly, Lane et al.[16] have demonstrated very long diagnostic delays, even after cardiac symptoms have appeared. This delay is greater than 4 years in 42% of patients with wtATTR-CM after having presented to the hospital a median of 17 times during the previous 3 years, whereas only one-third were diagnosed within 6 months of presenting with symptoms of cardiac origin.[16] Another study of 193 patients diagnosed with CA in Italy (87% had wtATTR-CM) showed that patients who had been diagnosed 6 or more months after symptom onset had a lower survival rate (median survival 30 months, 95% CI 22-37 months), whereas those with a diagnosis in under 6 months had a cumulative survival of 81%.[57] Notably, every month of delay after symptom onset was associated with a 5% increase in mortality risk.[57] "Red flags" utilization has been reportedly lower in patients with longer delays, and a longer diagnostic delay has been associated with higher NT-proBNP levels and worse symptoms.[16,58] Data on the impact of delay for patients and health systems are still limited, but these findings suggest that it is likely associated with a significant increase in the risk for adverse health outcomes, i.e., hospitalizations, mortality, inappropriate treatment, repeated specialist evaluations, and testing.[16,54,57]

Contemporary data also suggest that many patients receive a diagnosis for ATTR-CM after repeated medical visits,[1,17,19,48,49,59,60] suggesting that a large pool of patients with ATTR-CM seeks care in primary care settings (Fig. 1). The initial point of presentation depends on the nature of symptoms, and many specialists may have been involved for neurological, orthopedic, or unclear symptomatology.[60,61] Patients are primarily diagnosed after having developed cardiac symptoms, suggesting a considerable delay in presentation and diagnosis.[16] Those with comorbidities, advanced age, and non-specific symptoms may often present themselves to general practitioners and internists[62], and they are the most challenging to diagnose due to overlapping phenotypes. Misdiagnosing CA as HFpEF, aortic stenosis, or LV hypertrophy is common,[10,11,23] especially among the elderly,[63] leading to missed opportunities for disease modification.

**Table 1**
Challenges in the patient pathway of ATTR-CM.

| |
|---|
| Variable awareness / education across different medical specialists for ATTR-CM identification |
| Disease heterogeneity and systemic nature |
| Symptoms are non-specific and mimic other common disorders |
| Misperception of ATTR-CM as an untreatable disease |
| Lack of communication / care coordination |
| Occasional use of testing with insufficient sensitivity / specificity |
| Inconsistent follow-up of the recommended diagnostic algorithm |

## 3. Recommendations for improving the patient journey for ATTR-CM patients in Greece

The rapidly evolving landscape in the diagnosis and treatment of ATTR-CM has reemphasized the need to implement a holistic plan that will not only improve the patient journey through early detection and reduction of time-to-diagnosis but also address other related issues, such as improved screening, timely diagnosis, data collection, patient and caregiver support (Table 2). To that end, the European Union (EU) Council has identified the need for a comprehensive approach for addressing rare diseases and has issued a recommendation in 2009 for all EU member states to develop a strategy "to improve recognition and visibility of rare diseases, develop international links and pooled expertise, empower patient organizations and ensure sustainability of

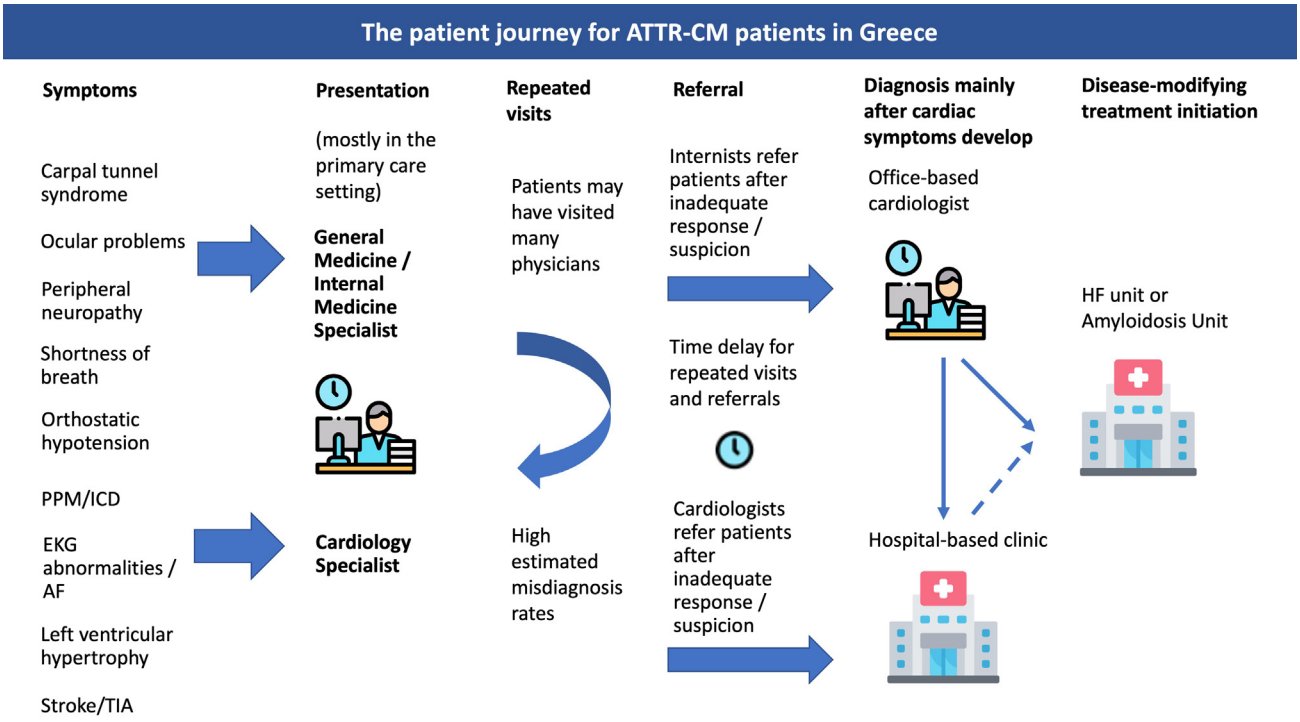


**Fig. 1.** The patient pathway for ATTR-CM in Greece.

information, research and care infrastructures."[64] Similarly, the UK has developed a Rare Diseases Framework after a national conversation with 6,293 responses among the rare disease community, with provisions for regular reports on progress and monitoring of key objectives.[65] The priorities of this action plan are a faster diagnosis, improved awareness of healthcare professionals, better care coordination, and facilitated access to expert care.[65] Similarly, the Rare 2030 foresight study, a European Parliament-led initiative, has provided eight recommendations broadly pertaining to earlier and more accurate diagnosis, access to high-quality healthcare, integrated and patient-centered care, patient engagement, needs-based research, and data optimization for the benefit of patients and society.[66] A Greek national plan for ATTR-CM could build upon existing practices and focus on the following key objectives.

### 3.1. Early diagnosis

Reaching a fast and correct diagnosis can change the prognosis of patients with ATTR-CM.[67] It leads to expert care and avoids a

**Table 2**
Recommendations for improving the patient journey for ATTR-CM in Greece.

| Objectives | Recommended actions |
|---|---|
| Reach an early diagnosis | - Improve physicians' awareness of the disease and education about disease-modifying therapy through innovative channels<br>- Include / upgrade ATTR-CM in the core medical training curriculum<br>- Screen for "red flag" findings (extracardiac and cardiac)<br>- Pursue etiological diagnosis<br>- Refer patients to specialized HF or amyloidosis units<br>- Ensure the availability of genetic testing<br>- Ensure availability of biomarkers (e.g., NT-proBNP) that may trigger the diagnostic process |
| Improve care coordination | - Facilitate collaboration between different specialists and access to expert care<br>- Promote patient-centric, integrated care models<br>- Establish diagnostic and therapeutic clinical pathways with provision for management of comorbidities<br>- Include social support provisions |
| Promote digital transformation and reference networks | - Embrace digital transformation to connect primary and expert care on a patient-centric model<br>- Establish uniform electronic health records<br>- Introduce decision support tools, e.g., reminders at the time of contact and virtual prescribing<br>- Monitor quality of care indicators<br>- Advance participation of Greek Centers in the European Reference Networks and encourage cross-border physician cooperation |
| Encourage patient engagement | - Support patient and caregiver participation in the design and execution of the disease management strategy<br>- Build awareness at community level<br>- Re-evaluate strategy regularly to respond to evolving patient needs |
| Advance rare disease registries | - Leverage data to improve diagnostic rates and minimize time-to-access to appropriate treatment<br>- Report progress in disease management<br>- Reduce variations in clinical practice<br>- Support research on country-relevant information |

cascade of repeated, inconclusive evaluations, which impose a strain on the physical, mental, and economic health of the patients and those around them. It is also a critical factor in the healthcare system's sustainability because a timely diagnosis could potentially prevent the spending of substantial resources.[16,54,57]

Upon clinical suspicion of CA, the diagnostic algorithm proposed by the most recent European position statement[67] should be applied in order to identify AL and ATTR CA, which currently account for the large majority of CA. This algorithm integrates the utilization of 99 mTc-DPD/PYP/HMDP scintigraphy with single photon emission computed tomography and quantification of serum free light chain, serum protein electrophoresis with immunofixation, and urine protein electrophoresis with immunofixation.[67] Negative assessment for monoclonal proteins suggests that AL amyloidosis is unlikely. If scintigraphy shows cardiac uptake Grade 2-3, ATTR amyloidosis can be diagnosed; if cardiac uptake is Grade 1, histological confirmation is required. If at least one of the monoclonal protein tests is abnormal, then AL amyloidosis has to be ruled out urgently, and a hematologic consultation is important. Under this scenario, further, CMR may be needed when scintigraphy is negative and/or histological evaluations to confirm the diagnosis and provide amyloid subtyping. Upon diagnosis of ATTR amyloidosis, genetic testing is advised to differentiate between hATTR and wtATTR. The Greek National Network of Precision Medicine in Cardiology includes six referral centers and four genotyping centers, which are interconnected and provide genetic testing and counseling for patients and their families.[68] Such centers of genotyping expertise should be supported to ensure streamlined access to diagnosis. Genetic testing is recommended even in patients of advanced age because a significant percentage may exhibit TTR mutations.[69] In the case of hATTR, the presence of cardiomyopathy, polyneuropathy, or both may warrant the application of additional therapeutics.[67] The island of Crete has been reported to have a high prevalence of hATTR (35.3/1,000,000), with p. Val50Met being the most frequent variant (63.3%), suggesting an additional need for increased awareness.[70]

To achieve a timely diagnosis, improved awareness and education of physicians are necessary.[71] Innovative educational resources (e.g., social media threads, podcasts, virtual meetings) may offer exposure to international expertise and support physicians in decision-making.[72,73] Novel educational interactive tools and case studies may assist in raising awareness and increase familiarization of doctors with the red flags of wtATTR-CM and their identification.[71] Particular focus should be given in the primary care setting with the inclusion of the extensive network of private and public outpatient clinics. The Greek healthcare setting is characterized by the presence of many specialists in primary care, i.e., 3,508 cardiologists and 4,604 internists in 2019 (cardiologists in Greece are estimated to be three times higher than the European average).[74] Most patients initially present themselves to primary care providers, and many of them visit different physicians in order to be diagnosed.[61] Their role is important in accelerating the time-to-diagnosis by recognizing the early manifestations of the syndrome, especially for those patients who present atypical symptoms at an early timepoint when organ infiltration is still amenable to treatment. Early referral to a specialist center for suspicious cases is not only recommended[67] but also ensures streamlined access to disease-modifying treatment.

Screening strategies should incorporate focused evaluation for “red flag” findings regardless of cardiac or extracardiac origin and should bridge clinical judgment across different specialties, e.g., internal medicine, cardiology, and hematology, through effective communication and coordination for assigning a diagnosis.[67] NT-proBNP utilization, as indicated, although not specific for ATTR-CM, may facilitate earlier involvement by cardiologists who could be triggered to search deeper in the differential diagnosis, especially when it is disproportionately elevated.[67]

Special attention should be given to the high rates of misdiagnosis, the need for etiological diagnosis, especially in atypical cases, and the importance of expanding treatment beyond symptom amelioration to disease modification. Identification and treatment of ATTR-CM should be upgraded as part of the professional medical education curriculum through specialized training modules for early suspicion and diagnosis, and particular consideration should be given to physicians who are trained in hospitals with occasional exposure to patients with rare diseases. Specialized training modules should also be provided to primary healthcare physicians[63] to support early suspicion and referral, as primary healthcare settings are being reformed to ensure a more prominent role in the overall healthcare provision landscape.[75] The UK Rare Diseases Action Plan 2022 has underlined the need to increase awareness of rare diseases among healthcare professionals.[76] One of the actions defined to achieve this is the publication of high-quality epidemiological and research studies to increase our understanding of rare diseases.[76]

### 3.2. Care coordination

The chronic trajectory of ATTR-CM, its association with aging, and the common existence of comorbidities imply that many patients require repeated medical treatment and social support.[16,49] This typically involves several medical appointments, laboratory testing, and hospitalizations for elective and/or urgent care. This significant burden of coordination falls on the patients and their caregivers. An integrated care model with well-defined clinical pathways,[29,67] structured coordination of different specialists, and specific nodes of referral[71] is essential to ensure proper delivery of care along with humanistic burden relief and cost minimization. The renewed focus on the primary setting following the introduction of new Greek legislation on equitable access and quality in primary healthcare[75] is an opportunity for different specialists to collaborate and share medical notes and concerns about imperfect diagnoses under an integrated care model. Many European countries have developed such models for rare diseases. For instance, Ireland has applied a holistic management plan that includes care pathways for diagnosis, treatment and social support provisions after receiving input from patients and caregivers.[77] Such a structured pathway should identify expert centers; provide access to educational information and social entitlements, such as disability benefits, caregivers’ allowance, and counseling; and ensure alignment with international quality standards.[77] Finally, the optimal utilization of regional and central resources, both in the diagnosis and follow-up, should be facilitated. Referral should be directed to an amyloidosis unit or a specialized HF unit with the option of close cooperation with hematologists. Undoubtedly, there is great value in referring patients to an amyloidosis center that mainly relates to staff expertise, imaging quality, and multidisciplinary teams.[71] However, the need for repeated traveling time to the central hospital increases the burden for patients and caregivers.[71] Thus, a collaborative model of care between primary and expert care,[67] where the patient is referred for diagnosis and treatment initiation and monitored locally, should be considered for ATTR-CM patients.

### 3.3. Digital transformation and reference networks

The ongoing process of digital transformation offers a unique opportunity to coordinate services and input from different providers. In the coontext of the "Recovery and Resilience Plan of Greece",[78] the expansion of screening programs and preventive services should ensure timely identification of ATTR-CM, along with the minimization of variations and inequalities in management.

Uniform electronic health records, which can be shared across specialties and reminders, can be set up in the e-prescribing system to assist physicians at the time and point of contact and virtual prescribing. Decision support systems present a great opportunity to highlight "red flags" in the therapeutic protocols and contribute to fewer missed diagnoses.[79] The potential usefulness of clinical decision support systems for rare diseases with difficult diagnostic approaches has been demonstrated in earlier studies.[80,81]

European reference networks (ERNs) are virtual networks of specialized units that pool expertise and resources to address complex or rare diseases.[82] The ERN program has received funding from many EU initiatives, such as the Health Program and Horizon 2020. We believe participation in such networks can offer significant benefits based on bi-directional collaboration, horizontally between expert centers and vertically with primary care partners.

### 3.4. Patient engagement

Improving patient engagement is another important element of a successful strategy. First, patient empowerment brings benefits at the individual level by encouraging appropriate and effective use of health resources, higher adoption of preventive services, and increasing patient satisfaction and QOL.[83] Second, at the macro level, patients can offer guidance to decision making through representative organizations and contribute to a learning and cost-effective health system.[83] There exists an EU council recommendation for the inclusion of patient organizations in the design of policies in rare diseases, who are expected to be present in plan development, monitoring, and assessment. Actions such as awareness raising, capacity building, and exchange of best practices and information are indicators of a successful national strategy for rare diseases.[64] Experience from other countries can offer significant insights as to the benefits of such engagement. Italy, Denmark, and the UK, among others, have taken important steps in incorporating patient feedback in designing rare disease strategies.[65,84] In particular, the Italian National Centre for Rare Diseases has developed a program of continuing education in rare disease patient identification, referral, and management addressed to general practitioners and other health professionals.[84] Additionally, they provide a number of courses, for patient organizations, with the goal of empowering patients with rare diseases and their families in the daily management of their disease. Through the Italian National Centre for Rare Diseases, patient organizations can participate in the promotion of targeted policies, research, and specific interventions for health and social care. In the UK, the new Rare Diseases Framework has been established, and its main approach has been to define priorities for the next 5 years by developing an engagement program in order to understand the main challenges of those living and working with rare diseases across the UK and how these challenges could be tackled.[65] In Denmark, a comprehensive plan for rare diseases was developed by a multi-stakeholder working group, with secured funding and post-implementation evaluation.[85] Among the actions to be implemented is the preparation of patient pathway descriptions for the most common rare diseases based on national and international guidelines of "best practice" to be adopted by the rare disease centers. In this context, Rare Diseases Denmark, a national alliance of 55 rare disease societies, provided recommendations such as the establishment of a helpline to offer free and anonymous support and counseling services to people with rare diseases and their families. It is evident that much of the progress in relationships between institutions and patients is the result of the work of patient organizations. Driven by the common necessity to overcome difficulties inherent in rare diseases, patient organizations encourage policy interventions and research that improve meaningful outcomes.[84] EURORDIS, a patient-driven alliance for rare diseases with a presence in 56 countries, has expressed the patient perspective in shaping recommendations by the EU Committee of Experts on Rare Diseases and the European Commission Expert Group on Rare Diseases[86] about quality assurance, care optimization, improved care pathways, registries, and codifications. Such an approach underpins the belief that access to medication is only one critical element of a successful strategy and addresses needs that contribute to a more efficient and effective care model. A strategy for ATTR-CM in Greece should be patient-centric and include social support provisions.

### 3.5. Rare disease registries

Patient registries may leverage data to improve diagnostic rates, reduce gaps in understanding disease heterogeneity, encourage research and collaboration across the scientific network, support clinical pathways, and potentially minimize wasteful use of resources while safeguarding data privacy.[87] They are a cost-effective way to monitor the natural history of a disease and unite involved parties to a common objective.[87] Under a predefined framework, they may also facilitate monitoring of implementation, audit, and revision of practice as part of a learning health system. The recent Food and Drug Administration guidance on rare diseases underpins the importance of natural history registries in reducing variations in clinical practice and improving treatment standards.[88] Many European countries have implemented national registries to facilitate earlier diagnosis of rare diseases.[89] For instance, Italy has established the national registry for rare diseases since 2001, which operates in multiple lines of activity: a) provides monitoring of rare diseases pertaining to updated epidemiology, diagnostic delay estimates, and health migration data, b) promotes preventive strategies, c) undertakes research initiatives, d) disseminates public information and e) carries out quality controls of genetic tests.[90] The Greek healthcare system is characterized by an extensive network of specialists involved in primary care, either public or private. A national registry that highlights key disease metrics and provides clarity in the evolving disease landscape could bridge silos of care, provide information on practice patterns, and potentially, improve clinical outcomes for patients with ATTR-CM.

## 4. Conclusion

ATTR-CM is a disease with a substantial patient, caregiver, and societal burden. The patient pathway is characterized by increased complexity pertaining to diagnostic pitfalls, delays in identification and referral, and a high need for additional physician evaluations. However, the introduction of disease-modifying treatment has created a paradigm shift in ATTR-CM management. The urgency to reveal this hidden entity and optimize the patient journey constitutes the contemporary unmet need. The Greek healthcare system needs to integrate collaboration between different specialists, bridge the primary and expert care settings, and advance communication by leveraging the features of digital transformation. We need to encourage the training of our health providers in ATTR-CM, which will increase the degree of suspicion about the existence of ATTR-CM, promote etiological diagnosis and, ultimately, provide the pathway to more effective care.

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## Conflict of interest

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