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# Diagnosis and treatment of hereditary transthyretin amyloidosis with polyneuropathy in the United States: Recommendations from a panel of experts

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## Abstract

Hereditary transthyretin (ATTRv; v for variant) amyloidosis is a rare, multisystem, progressive, and fatal disease in which polyneuropathy is a cardinal manifestation. Due to a lack of United States (US)-specific guidance on ATTRv amyloidosis with polyneuropathy, a panel of US-based expert clinicians convened to address identification, monitoring, and treatment of this disease. ATTRv amyloidosis with polyneuropathy should be suspected in unexplained progressive neuropathy, especially if associated with systemic symptoms or family history. The diagnosis is confirmed through genetic testing, biopsy, or cardiac technetium-based scintigraphy. Treatment should be initiated as soon as possible after diagnosis, with gene-silencing therapeutics recommended as a first-line option. Consensus is lacking on what represents "disease progression" during treatment; however, the aggressive natural history of this disease should be considered when evaluating the effectiveness of any therapy.

**KEYWORDS**
ATTRv amyloid neuropathy, ATTRv amyloidosis with polyneuropathy, diagnosis guidelines, hereditary transthyretin-mediated (hATTR) amyloidosis, treatment recommendations

**Abbreviations:** $^{99m}$Tc, technetium-99 m; AFO, ankle foot orthoses; AL, amyloid light chain; ALS, amyotrophic lateral sclerosis; ASO, antisense oligonucleotide; ATTRv, hereditary transthyretin (v for variant); ATTRwt, wild-type transthyretin; BNP, brain natriuretic peptide; BP, blood pressure; CHF, chronic heart failure; CIDP, chronic inflammatory demyelinating polyneuropathy; CNS, central nervous system; COMPASS-31, Composite Autonomic Symptom Score-31; CTS, carpal tunnel syndrome; EF, ejection fraction; eGFR, estimated glomerular filtration rate; FAP, familial amyloid polyneuropathy; FDA, US Food and Drug Administration; GI, gastrointestinal; hATTR, hereditary transthyretin-mediated; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; IBS, irritable bowel syndrome; IVIg, intravenous immunoglobulin; mRNA, messenger ribonucleic acid; N/A, not applicable; NIS, neuropathy impairment score; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; NT-proBNP, *N*-terminal pro-brain natriuretic peptide; PND, polyneuropathy disability; PYP, pyrophosphate; QST, Quantitative Sensory Testing; QT, QT interval; RISC, RNA-induced silencing complex; RNAi, ribonucleic acid interference; RNase H, ribonuclease H; R-ODS, Rasch-built Overall Disability Scale; siRNA, small interfering ribonucleic acid; THAOS, Transthyretin Amyloidosis Outcomes Survey; TTE, transthoracic echocardiogram; TTR, transthyretin; US, United States; VP, ventriculoperitoneal; wt, wild-type.

## 1 | INTRODUCTION

Hereditary transthyretin (ATTRv; v for variant) amyloidosis, also known as hATTR amyloidosis, is a rare, progressive, debilitating, and fatal disease caused by pathogenic variants in the transthyretin (*TTR*) gene.[1–4] TTR is produced primarily in the liver and circulates as a stable tetrameric protein involved in the transport of vitamin A and thyroxine.[1,5,6] Pathogenic *TTR* variants increase the susceptibility of TTR tetramers to dissociate to monomers and to proteolyze into TTR fragments.[7–9] These dissociated proteins misfold to form amyloid deposits, which accumulate in and cause damage to multiple organs and tissues, including nerves, heart, gastrointestinal (GI) tract, and musculoskeletal tissues.[1,2,4] ATTRv amyloidosis is thus a multisystem disease,[4,10–12] with the majority of patients having a mixed phenotype of polyneuropathy and cardiomyopathy.[13,14] Without treatment, it follows a progressive course, with deterioration in patient quality of life and physical functioning. Survival rates can vary according to disease characteristics, with the median survival from disease onset being greater in patients presenting before age 50 years compared with late-onset disease (10–20 vs. ~7 years, respectively),[15–18] and with a Val30Met genotype compared with a non-Val30Met genotype (12.1 vs. 6.3 years, respectively).[19]

Clinicians may overlook ATTRv amyloidosis because of its variability in presenting symptoms, gene penetrance, and natural course of the disease, leading many patients to experience diagnostic and treatment delays.[20–24] Diagnostic algorithms and treatment recommendations for cardiac amyloidosis have been published on behalf of the American Heart Association,[25,26] although in the United States (US) there is a lack of specific guidance for recognizing symptoms of ATTRv amyloidosis with polyneuropathy. Part of the challenge in the US is that many genetic variants are present and there is no characteristic disease presentation, unlike endemic regions (e.g., Portugal, Brazil, and Japan).[23,27] Hence, a US-relevant guideline is needed.

Furthermore, and despite the advancement in therapeutic modalities,[28–30] there are no guidelines for optimal disease management in patients with ATTRv amyloidosis and polyneuropathy, or for which therapies may be more suitable when disease progresses.

This expert opinion article addresses these needs, providing US-specific insights into disease awareness, diagnosis, monitoring, and guidance on the most appropriate treatments for ATTRv amyloidosis with polyneuropathy.

## 2 | PURPOSE AND METHODOLOGY

In February 2022, we, a group of seven neurologists with expertise in ATTRv amyloidosis in the US, convened a virtual roundtable. We discussed the pooled responses from a premeeting questionnaire that was developed by Adelphi Communications Ltd (Bollington, UK), independently of the sponsor Alnylam® Pharmaceuticals (Cambridge, MA), following a literature review (electronic database searches [National Center for Biotechnology Information PubMed]) of expert recommendation articles, natural history studies, clinical trials outcome data, and non-US management guidelines in ATTRv amyloidosis with polyneuropathy. The roundtable discussions informed a set of recommendations on red-flag symptoms, diagnosis, monitoring, and treatment of patients with ATTRv amyloidosis with polyneuropathy in the US, which were further refined over four rounds of feedback, with the aim to (1) provide guidance on recognizing patient history and symptoms suggestive of ATTRv amyloidosis, and identifying best practice for further investigation and confirming diagnosis; (2) provide guidance on monitoring presymptomatic *TTR* variant carriers or symptomatic patients with ATTRv amyloidosis with polyneuropathy; (3) provide guidance on the most appropriate disease-modifying and disease management treatments for ATTRv amyloidosis with polyneuropathy; and (4) identify best practice for monitoring disease progression while on treatment. Where noted, strength of recommendations was categorized as Class I = strong, Class IIa = moderate, Class IIb = weak, based on the agreement of all experts, four or more, and less than four, respectively.

## 3 | RESULTS

### 3.1 | Symptoms and clinical presentation of ATTRv amyloidosis with polyneuropathy

Over 140 pathogenic TTR variants have been identified worldwide,[31,32] with the frequency of each varying across different geographic locations. A mixed phenotype develops with most variants,[13,14,33] although some have been associated with a genotype–phenotype trend. The Transthyretin Amyloidosis Outcomes Survey (THAOS) registry reported over 30 different pathogenic TTR variants in the US, the most common being Val122Ile (45%), Thr60Ala (20%), and Val30Met (6%).[34] The V122I variant is reported in 3–4% of Black Americans,[35,36] and although penetrance varies, it is possible that improved disease awareness may lead to an increased rate of diagnosis in these individuals.

A consequence of the genetic heterogeneity in the US is that it is difficult to define a "typical presentation", and presenting symptoms can be variable. Table 1 lists possible presenting neurologic signs and symptoms and other organ manifestations (non-neurologic) in the US, as observed by the authors in patients with ATTRv amyloidosis. Some less common presentations of ATTRv amyloidosis include bulbar complications (i.e., speech and swallowing difficulties, hoarseness), ocular manifestations (i.e., together with vitreous opacities), urinary bladder dysfunction (i.e., hematuria, irritative and obstructive symptoms), renal disease, and myopathy. This range of manifestations across several different organs or body systems underscores the diagnostic challenges of ATTRv amyloidosis in the US, in addition to highlighting the benefit of multispecialty teams.

As there are no specific signs or symptoms of polyneuropathy that are unique to ATTRv amyloidosis, its occurrence should be considered in the context of additional red flags of accompanying

**TABLE 1** Possible neurologic and non-neurologic manifestations of ATTRv amyloidosis.

| **Symptoms of neuropathy (neurologic)** | | | |
|---|---|---|---|
| **Sensory** | **Motor** | **Autonomic** | |
| Pain (stabbing, shocks, contact allodynia, burning) | Distal muscle weakness and atrophy (unless superimposed myopathy) | Erectile dysfunction | |
| Altered sensation (touch or temperature) | Tripping | Lightheadedness/orthostatic hypotension/syncope/presyncope | |
| Tingling, prickling sensations | Foot drop | Genitourinary problems (incontinence, incomplete emptying, increased urinary frequency) | |
| Imbalance | Walking difficulties | GI manifestations (diarrhea, constipation, early satiety, motility dysfunction)[a] | |
| | Difficulty opening jars | Loss of hair/sweating abnormalities | |
| | Loss of dexterity | Heat intolerance | |
| | Difficulty climbing stairs/getting up off a chair | Blurred vision, dry eyes | |
| | | Dry mouth | |
| **Signs/symptoms from other organs/body systems (non-neurologic)** | | | |
| **Cardiac** | **Musculoskeletal** | **Ophthalmologic** | **Renal** |
| Features of hypertrophic cardiomyopathy | CTS, most often bilateral | Vitreous opacities | Renal failure |
| HFpEF | Dupuytren's contracture | Glaucoma | Proteinuria |
| Arrhythmia | Rotator cuff injury | Dry eyes | Hematuria |
| Peripheral edema | Lumbar stenosis | Abnormal conjunctival vessels | |
| Shortness of breath | Tendon rupture | Cataracts | |

Abbreviations: ATTRv, hereditary transthyretin (v for variant); CTS, carpal tunnel syndrome; GI, gastrointestinal; HFpEF, heart failure with preserved ejection fraction.

[a]GI manifestations in ATTRv amyloidosis can also be of nonautonomic origin, with deposition of amyloid within the GI system resulting in symptoms such as abdominal pain, esophageal reflux, nausea, constipation, and early satiety.

symptoms (Table 1), other medical conditions, prior medical history, and family history, which may all support the suspicion of ATTRv amyloidosis.

### 3.1.1 | Red flags for raising suspicion of ATTRv amyloidosis

For patients presenting with neurologic signs/symptoms, the most important red flags for raising suspicion of ATTRv amyloidosis are the rate of neuropathy progression and/or accompanying comorbidities, particularly concurrent or prior carpal tunnel syndrome (CTS), autonomic failure, GI dysmotility, and heart failure with preserved ejection fraction (Table 1 and Figure 1).

Based on the outcomes of clinical studies reported in a recent meta-analysis, patients with ATTRv amyloidosis typically experience a rapid neurologic progression (worsening of $\sim +12$ points per year in neuropathy impairment score [NIS]) compared with other conditions such as diabetic neuropathy (+0.6–1.2 NIS points/year), Charcot–Marie–Tooth disease (+1.4 NIS points/year), or idiopathic neuropathy.[37] A notable exception is people with Val122Ile variants, who typically have a mild polyneuropathy.[38] We also identified motor weakness early in the course of neuropathy or predominant motor weakness as key differentiating factors.

Median neuropathy at the wrist (CTS) is prominent in ATTRv amyloidosis due to amyloid deposition in the flexor tenosynovium and transverse carpal ligament.[39] Although common in the general population, in patients with ATTRv amyloidosis it is more often bilateral, more refractory to treatment, and more prone to recurrence after CTS release than in patients with idiopathic CTS.[40,41] CTS may precede the onset of neurologic symptoms by between 7 and 10 years, and as such a detailed review of medical history is advised, especially in those patients with no known family history of ATTRv amyloidosis.[24,41] Furthermore, CTS-induced hand weakness is not a common feature in most length-dependent neuropathies, and in combination with sensory neuropathy would raise suspicion of ATTRv amyloidosis.

Autonomic dysfunction due to small-fiber neuropathy can be one of the earliest manifestations in patients with ATTRv amyloidosis, often preceding the development of overt neurologic symptoms.[42] Autonomic symptoms are often missed if not specifically queried, or alternatively can be dismissed as inconsequential (e.g., intermittent GI symptoms of recurrent diarrhea diagnosed as irritable bowel syndrome) or as a typical age-related event (e.g., erectile dysfunction).

Of the manifestations from other body systems that may occur concurrently with neuropathy (Table 1 and Figure 1), those that are musculoskeletal in nature are particularly noteworthy. In addition to CTS (as previously discussed), these musculoskeletal manifestations

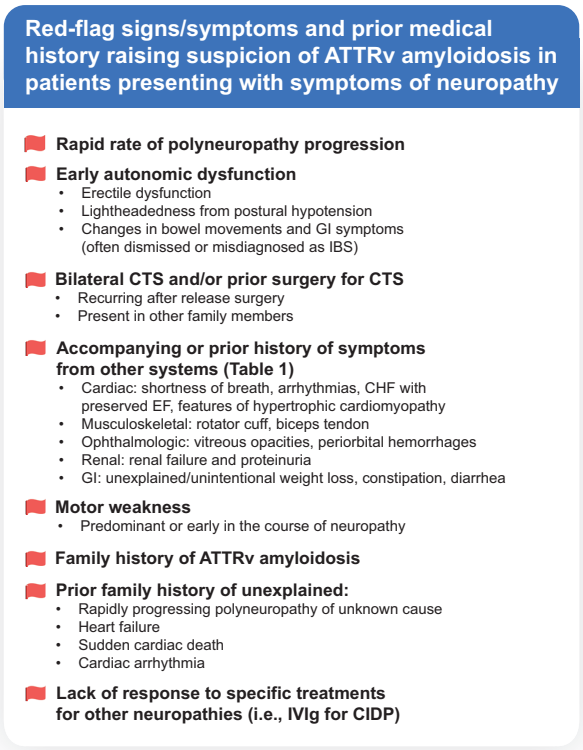


**FIGURE 1** Factors raising suspicion of ATTRv amyloidosis with polyneuropathy in the US. ATTRv, hereditary transthyretin (v for variant); CHF, chronic heart failure; CIDP, chronic inflammatory demyelinating polyneuropathy; CTS, carpal tunnel syndrome; EF, ejection fraction; GI, gastrointestinal; IBS, irritable bowel syndrome; IVIg, intravenous immunoglobulin; US, United States.

are also common in patients with wild-type (wt) transthyretin (ATTRwt; nonvariant *TTR*) amyloidosis.[43–45]

Other relevant family history or prior medical history includes long-standing idiopathic peripheral neuropathy that does not respond to specific treatments for other neuropathies; rapidly progressing idiopathic polyneuropathy, particularly occurring in young patients; and sudden cardiac death, cardiac arrhythmia, vitreous opacities, or heart failure with preserved ejection fraction, which is commonly seen in patients with cardiac amyloidosis.[25]

The active consideration of red-flag signs and symptoms, together with the insight into typical patterns of symptom presentation, will improve recognition of ATTRv amyloidosis with polyneuropathy among index patients as well as affected family members and known asymptomatic variant carriers.

## 3.2 | Making a diagnosis of ATTRv amyloidosis with polyneuropathy

Early diagnosis of ATTRv amyloidosis is critical; initiating treatment early can prevent organ damage that can be irreversible. Unfortunately, diagnosis is often delayed because many of the neurologic symptoms are nonspecific and are often misdiagnosed as other conditions (e.g., chronic inflammatory demyelinating polyneuropathy, diabetic neuropathy, motor neuron disease, and idiopathic neuropathy).[46–48] Table 2 lists the most common misdiagnoses alongside possible differentiating factors to consider for suspicion of ATTRv amyloidosis when faced with different neuropathy phenotypes.

### 3.2.1 | Making a diagnosis of ATTRv amyloidosis with polyneuropathy: Genetic and laboratory testing

For confirming diagnosis following suspicion of ATTRv amyloidosis, and for differentiating from other conditions, genetic testing/panel screening is a key tool. For patients with unexplained progressive peripheral neuropathy, even with no additional red flags indicative of ATTRv amyloidosis, testing for a panel of genes and/or laboratory screening can help exclude other causes of neuropathies (e.g., genetic conditions, vitamin deficiencies, diabetes, or amyloid light chain [AL] amyloidosis).[49,50] Genetic counseling should occur before genetic testing of an individual suspected of having ATTRv amyloidosis, and if a *TTR* variant is identified, this should be extended to the individual's at-risk family members who may be carriers of *TTR* variants.

### 3.2.2 | Making a diagnosis of ATTRv amyloidosis with polyneuropathy: Tissue biopsy

In the US, where disease presentation is more variable and *TTR* variants may be less penetrant than in endemic areas, a diagnosis of ATTRv amyloidosis may not always be reached based on a confirmed *TTR* variant alone, as other co-existing conditions can lead to similar symptoms. Thus, a tissue biopsy to confirm TTR amyloid deposition is recommended for accurate diagnosis.

In an individual with a confirmed *TTR* variant who is in the earlier stages of disease and exhibits only mild sensory neuropathy symptoms with normal electrodiagnostic testing, a biopsy can provide the

**TABLE 2** Common misdiagnoses for patients diagnosed with ATTRv amyloidosis.

| Neuropathy phenotype or manifestation | Common misdiagnoses | Factors informing decision to perform differential diagnostic assessment | Characteristics that may indicate ATTRv amyloidosis |
|---|---|---|---|
| Length-dependent peripheral neuropathy | • Diabetic neuropathy<br>• Idiopathic neuropathy<br>• Alcohol neuropathy | • Mild diabetes with severe neuropathy<br>• Weakness with sensory abnormalities; rapid progression<br>• Concurrent development of other symptoms (erectile dysfunction, change in bowel habits); history of other conditions (e.g., unexplained weight loss) | • Concurrent cardiac disease<br>• Nerve biopsy findings<br>• Early motor involvement<br>• Previous or concurrent CTS<br>• Concurrent cardiac history: CHF, arrhythmia, or syncope |
| Demyelinating neuropathy | • CIDP | • Primarily axonal polyneuropathy; no or poor response to prior immunotherapy; accompanying autonomic symptoms<br>• Family history, or other amyloid complication | |
| Motor neuropathy | • Motor neuron disease/ALS<br>• CIDP | • Concurrent sensory component | • Other organ involvement<br>• Prominent sensory symptoms distinguishes from ALS |
| Small-fiber neuropathy | • Fibromyalgia<br>• Idiopathic small-fiber neuropathy | • Other associated features of ATTRv amyloidosis<br>• Small-fiber neuropathy rapidly progressing to mixed-fiber (small and large) neuropathy | • Other organ involvement; constellation of red-flag symptoms |
| Bilateral CTS | • Occupational CTS | • New-onset CTS despite no recent work history/history of repetitive motions<br>• Presence of other complications (e.g., HF) | • Concurrent idiopathic neuropathy or autonomic dysfunction<br>• Trigger finger; lumbar stenosis<br>• Recurrent CTS |
| Unexpected weight loss | • Malignancy or autoimmune disease | • Other associated features of ATTRv amyloidosis | |

Abbreviations: ALS, amyotrophic lateral sclerosis; ATTRv, hereditary transthyretin (v for variant); CHF, chronic heart failure; CIDP, chronic inflammatory demyelinating polyneuropathy; CTS, carpal tunnel syndrome; HF, heart failure.

information necessary to confirm an ATTRv amyloidosis diagnosis. Similarly, biopsy confirmation of amyloid deposition and type is useful in situations where confounding comorbidities are present. For example, an individual with a confirmed *TTR* variant may have concurrent diabetes or have an abnormal result on serum protein electrophoresis, raising the possibility of AL amyloidosis. A biopsy can confirm if amyloid is present (indicating the cause of the neuropathy), and mass spectrometry or immunohistochemical analysis of the biopsy sample can differentiate between TTR and AL.

If a biopsy is considered, we recommend collecting tissue from a patient with suspected ATTRv amyloidosis who is undergoing any invasive procedure (e.g., CTS release surgery or GI endoscopy). A liaison with the physician performing the procedure to obtain a suitable biopsy sample will avoid unnecessary repeat procedures and expedite a diagnosis. Otherwise, tissue biopsy samples can be obtained either directly from the clinically affected organ (e.g., heart or nerve) or preferably from more easily accessible tissues such as skin, abdominal fat pad, labial salivary glands, or the rectum. Of these, skin biopsies are easily accessible and practical.[51] It should be noted that because of the sporadic nature of amyloid distribution,[52] the overall sensitivity and accuracy of tissue biopsies can vary according to tissue type (50–80% in fat pad aspirate,[53] 70% in skin biopsies,[51] dependent on study and center, to ~100% in cardiac tissue), tissue sampling/processing, and the expertise of the center at which the histopathologic test is performed.[54] As such, the initial biopsy site should be selected depending on the feasibility, expertise, and yield of tissue from the specific organ, as well as expertise according to the center where the procedure is performed. We recommend caution in interpretation of biopsy results as a negative biopsy in a patient with a high suspicion of ATTRv amyloidosis should not definitively exclude a diagnosis, and further investigation (including potential repeat biopsy, or biopsy of a different tissue or organ) is warranted.

In the absence of a definitive biopsy result, the clinician should also consider cardiac technetium ($^{99m}$Tc)-based tracer scintigraphy scanning ($^{99m}$Tc-pyrophosphate [PYP] or $^{99m}$Tc-3,3-diphosphono-1,2-propanodycarboxylic acid) as a method to detect TTR amyloid, dependent on center availability. Here, the combined result of a positive Grade 2 or 3 myocardial uptake of radiotracer (strong cardiac uptake with mild/absent bone uptake) scan, and the absence of a clonal plasma

**TABLE 3** Recommended assessments/tools for staging or monitoring neurologic symptoms in patients with symptomatic or presymptomatic ATTRv amyloidosis.

| Assessment of neurologic symptoms | | | |
|---|---|---|---|
| **Assessment tool** | **Strength of recommendation[a]** | **Sensitivity to disease progression (1–3)[b]** | **Recommended frequency** |
| Neurologic examination or NIS | I | 1/2 | 6–12 months |
| Electrodiagnostic testing | I | 2/3 (does not detect small-fiber neuropathy) | Always recommended for new patient/initial assessment at baseline; can be repeated if normal every 1–2 years in presymptomatic variant carriers<br>Some centers perform only if new symptoms indicative of radiculopathy or CTS, following initial diagnosis<br>Some centers will perform annually |
| Orthostatic BP/vitals | IIa | 2 | New patient/annually to assess treatment response |
| Autonomic reflex screen | IIb | 2 | New patient |
| PND/FAP staging | I | 3 | Annual |
| R-ODS questionnaire | I | 1/2 | Annual/every 6 months by those that use in clinical practice<br>Most centers perform only for clinical trials |
| Norfolk QOL-DN questionnaire | IIb | 1 | Annual/every 6 months by those that use in clinical practice<br>Most centers perform only for clinical trials |
| COMPASS-31 questionnaire | IIa | 2 | Annual/every 6 months by those that use in clinical practice<br>Most centers perform only for clinical trials |
| Skin biopsy | I | 1 (can additionally document presence of amyloid) | New patient/initial assessment/as needed |
| QST | IIb | 2 | Every 6–12 months for those that use in clinical practice |

Abbreviations: ATTRv, hereditary transthyretin (*v* for variant); BP, blood pressure; COMPASS-31, Composite Autonomic Symptom Score-31; CTS, carpal tunnel syndrome; FAP, familial amyloid polyneuropathy; NIS, neuropathy impairment score; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; PND, polyneuropathy disability; QST, Quantitative Sensory Testing; R-ODS, Rasch-built Overall Disability Scale.
[a]Class I = strong; Class IIa = moderate; Class IIb = weak.
[b]1 = very sensitive; 2 = sensitive; 3 = moderately sensitive.

cell process as assessed by serum free light chains and serum and urine immunofixation, has shown a positive predictive value of ~100% to confirm transthyretin (ATTR) amyloidosis.[55–57] Thus, in cases where a *TTR* variant is confirmed by genetic testing and the patient has manifestations of the disease alongside a Grade 3 scan indicating TTR amyloid (and no evidence of AL amyloidosis) and no other cause for polyneuropathy, physicians may make a diagnosis of ATTRv amyloidosis with polyneuropathy without a biopsy confirmation.

### 3.2.3 | Making a diagnosis of ATTRv amyloidosis with polyneuropathy: Asymptomatic carrier to symptomatic patient

Not all *TTR* variant carriers will develop the disease, and some individuals will remain asymptomatic. The presence of a *TTR* variant does not indicate active disease; therefore, monitoring presymptomatic patients from an established baseline ahead of their predicted age of onset may allow for early diagnosis. The age of disease onset in a *TTR* variant carrier may be predicted from the typical age of onset for a specific genotype, whether the patient is from an endemic or nonendemic region, and/or evaluation of age of onset in family members.[58,59] In the US, a family history is less common, and therefore knowledge and education around the typical age of onset for specific variants are important. Monitoring should begin ~5–10 years ahead of the predicted age of onset to determine a "baseline" for the patient; however, earlier assessment would be required if obvious symptoms develop. Frequency of follow-up assessments can vary depending on variant type and expected rate of progression, but in general should occur approximately every 1–2 years, focusing on cardiac and neurologic involvement, as well as other complications (recommended assessments/tools and frequency for monitoring are given in Tables 3 and 4). To ensure symptoms are recognized early and to trigger assessment, *TTR* variant carriers—in particular those without a family history of disease—should be educated regarding common symptoms of ATTRv amyloidosis.

The decision flowchart including our recommendations (Figure 2) can be used to guide diagnosis on a case-by-case basis.

**TABLE 4** Recommended assessments/tools for staging or monitoring non-neurologic symptoms in patients with symptomatic or presymptomatic ATTRv amyloidosis and cardiac involvement.

| Assessment of non-neurologic symptoms[c] | | | |
|---|---|---|---|
| **Assessment tool** | **Strength of recommendation[a]** | **Sensitivity to disease progression (1–3)[b]** | **Recommended frequency** |
| Biomarkers | | | |
| BNP | IIa | 2 | Initial evaluation/follow-up dependent on progressive symptoms |
| NT-proBNP | I | 2 | Annually |
| Troponin I | I | 1 | Annually |
| Prealbumin[d] | IIa | N/A | At baseline and annually to monitor response to treatment |
| Echocardiography/TTE | I | 1 | Frequency will be determined on a case-by-case basis depending on the clinical picture; can be performed at baseline screening assessment |
| Scintigraphy (PYP) | I | 1 | Initial evaluation; follow-up dependent on progressive symptoms |
| Cardiac MRI | IIa | 1/2 | Available option if other cardiac assessments are inconclusive |
| Kidney function (i.e., eGFR), urine protein | I | 2 | Annual |

Abbreviations: ATTRv, hereditary transthyretin (v for variant); BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; N/A, not applicable; NT-proBNP, *N*-terminal pro-brain natriuretic peptide; PYP, pyrophosphate; TTE, transthoracic echocardiogram; TTR, transthyretin.
[a]Class I = strong; Class IIa = moderate; Class IIb = weak.
[b]1 = very sensitive; 2 = sensitive; 3 = moderately sensitive.
[c]Clinicians should consider a collaborative multispecialty approach to assessment of non-neurologic symptoms to capture the multisystem nature of this disease.[91]
[d]In patients receiving TTR silencers, prealbumin testing to monitor TTR suppression may provide some reassurance of pharmacologic response to treatment for some patients.

## 4 | TREATMENT INITIATION TIMING AND DISEASE MONITORING

### 4.1 | Timing of treatment initiation

Long-term extension studies of pharmacotherapies approved in the US for ATTRv (or hATTR) amyloidosis with polyneuropathy (patisiran Global OLE[60] and inotersen NEURO-TTR LTE[61]) indicated that early intervention with disease-modifying therapies results in better patient outcomes. Patients who had been previously treated with placebo in Phase 3 studies of patisiran and inotersen demonstrated improvement or stabilization in measures of polyneuropathy following initiation of disease-modifying therapy in the respective long-term studies, although the level of neurologic function observed in these patients did not reach that observed in patients who had received earlier active treatment. Clinicians should initiate treatment in patients as soon as possible following a diagnosis of ATTRv amyloidosis with polyneuropathy.

In the future, biomarkers may provide additional evidence of active neurologic damage, with ongoing studies suggesting that neurofilament light chain[62–64] has a potential future application for the early detection of nerve damage in patients with ATTRv amyloidosis, thereby facilitating identification of patients transitioning from carrier to symptomatic disease.

### 4.2 | Monitoring of disease in ATTRv amyloidosis

Typically, the natural course of ATTRv amyloidosis with polyneuropathy is characterized by progressive disability (familial amyloid polyneuropathy [FAP]): FAP Stage 1, sensory polyneuropathy; FAP Stage 2, progressive walking disability; and FAP Stage 3, wheelchair bound or bedridden.[65,66] Manifestations in other affected organs also worsen over the course of disease.[4,67] Our recommended tools and assessments for monitoring disease progression in presymptomatic patients and symptomatic patients with either neurologic or cardiac involvement are given in Tables 3 and 4, respectively.

We recommend a neurologic assessment for monitoring patients, which includes symptoms of gait, weakness, risk of falls, lightheadedness, GI issues, weight loss, and how the patient is feeling, along with a detailed neurologic examination (Table 3), every 6–12 months.[11] Additional objective assessments such as electrodiagnostic testing as well as patient-focused symptomatic questionnaires (Table 3) should be obtained at baseline and repeated when clinically indicated (e.g., new neurologic symptoms).[11,59]

If electrodiagnostic studies are repeated, care must be taken to replicate exact conditions (i.e., temperature, distances, testing center, and technique) to ensure that any decrease in the compound muscle action potential or sensory nerve action potential amplitude is accurate and clinically meaningful.

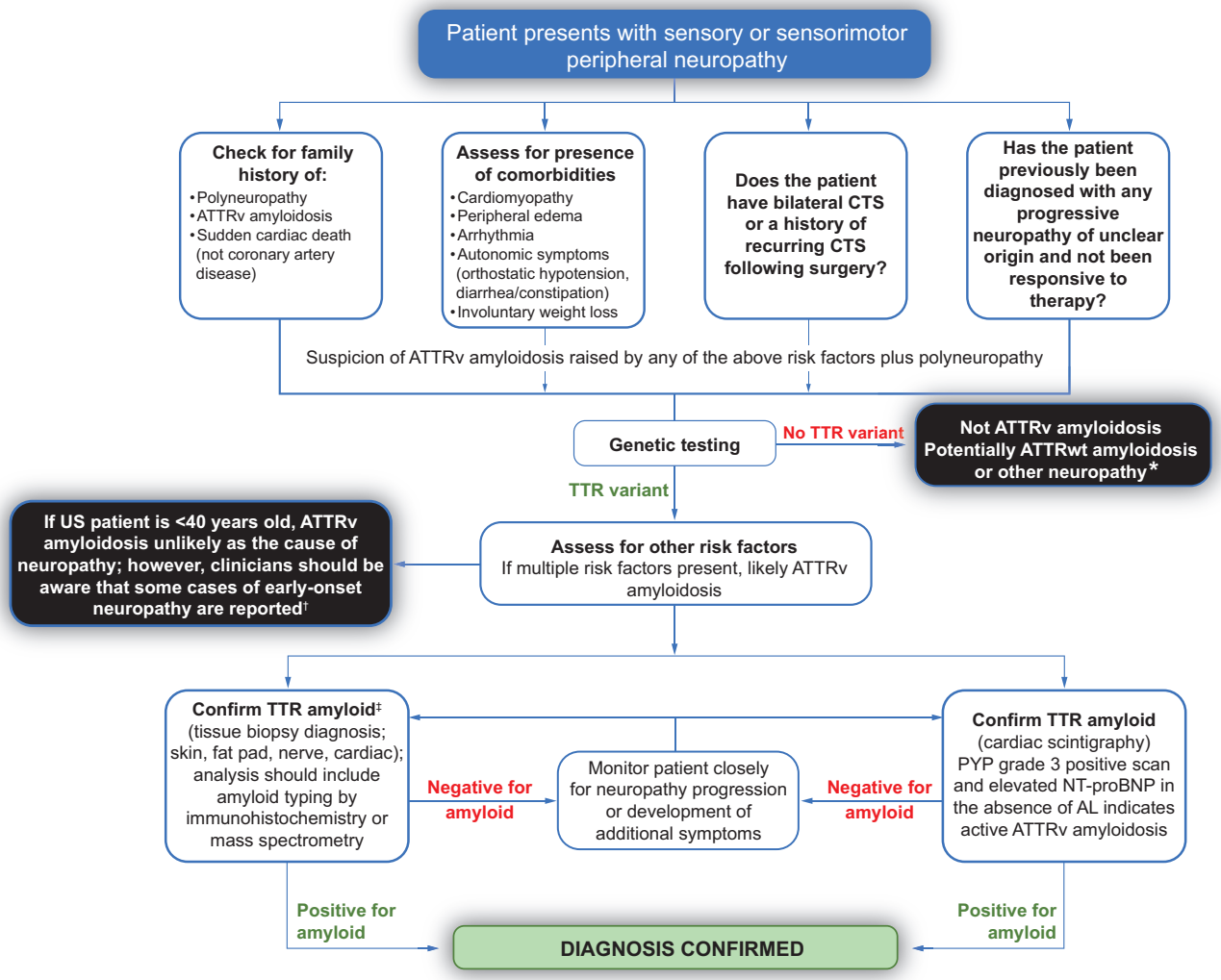


**FIGURE 2** Key considerations and recommended assessments for diagnosis of ATTRv amyloidosis with polyneuropathy in the US. *Patients may be assessed for genetic conditions including Charcot–Marie–Tooth disease and hereditary neuropathy with liability to pressure palsies, or screened for vitamin B12 deficiency, diabetes (hemoglobin A1C assessment), thyroid dysfunction, monoclonal gammopathy (immunofixation electrophoresis), or AL amyloidosis (immunoglobulin free light chain assessment). †Early onset of polyneuropathy has been reported in ATTRv amyloidosis.[92] ‡Importance of tissue diagnosis is greater when concurrent possible causes of peripheral neuropathy (i.e., B12 deficiency, diabetes mellitus, paraproteinemia, etc.) are present. In certain cases where there is no alternative cause for a progressive neuropathy, especially when multisystem features are present, a biopsy may not be necessary. A negative tissue biopsy in a patient with a high suspicion of ATTRv amyloidosis does not exclude a diagnosis, and further investigation (i.e., scintigraphy) or close follow-up is warranted. AL, amyloid light chain; ATTRv, hereditary transthyretin (v for variant); ATTRwt, wild-type transthyretin; CTS, carpal tunnel syndrome; NT-proBNP, *N*-terminal pro-brain natriuretic peptide; PYP, pyrophosphate; TTR, transthyretin; US, United States.

Patient-reported tools may also be useful for monitoring disease progression as they are easy for the patient to complete and are personally reflective of their symptoms. In particular, the Norfolk Quality of Life-Diabetic Neuropathy questionnaire[68] includes questions specifically relating to polyneuropathy symptoms of pain at different body locations, sensory disturbances, and autonomic dysfunction, and the Rasch-built Overall Disability Scale[69] provides a broader overview of a patient's ability to perform activities of daily living (e.g., washing up or walking up a flight of stairs). The Composite Autonomic Symptom Score-31 questionnaire evaluates the impact of autonomic symptoms across six domains (orthostatic intolerance, vasomotor, secretomotor, GI, bladder, and pupillomotor) and is an accurate tool for assessing the onset and follow-up of all manifestations of dysautonomia individually.[70] An increasing number of clinical studies for ATTRv amyloidosis are including patient-reported measures as endpoints due to their clinical importance.

Specific clinical tests for monitoring autonomic dysfunction are not commonly performed in many clinics, but standard tests for

orthostatic hypotension, a hallmark of autonomic dysfunction, are simple and easy to perform and should be routinely undertaken at an initial clinical assessment where possible. Heart rate variability is considered a sensitive, although not specific, marker of cardiac autonomic dysfunction. Indeed, although it is typically easy to perform, interpretation of the output must consider any concomitant cardiac involvement or medications. Twenty-four-hour blood pressure monitoring is an easy test that can document labile blood pressure, orthostatic changes, and dysregulation in the circadian cycle when a nighttime blood pressure dip is reduced or absent. More specific autonomic tests should be performed at specialized centers and may be considered in patients with nonspecific symptoms to confirm autonomic dysfunction.

## 5 | TREATMENT CHOICE FOR ATTRV AMYLOIDOSIS WITH POLYNEUROPATHY IN THE US

A key part of disease management for patients diagnosed with ATTRv amyloidosis includes symptomatic treatments, which can reduce symptom burden but do not affect the underlying disease pathophysiology. Available treatments for symptomatic relief (listed in Table 5) range from providing physical therapy for improving gait and balance, to supporting devices (i.e., splints, ankle foot orthoses), and/or to different drugs for amelioration of specific symptoms (e.g., pain, GI manifestations, orthostatic hypotension).

Other than symptomatic treatment, there has been a notable increase in the range of disease-modifying treatment strategies investigated over the last 10–15 years, whereas previously liver transplantation was the only established treatment available. In addition to the underlying complications of the procedure, liver transplantation has variable efficacy across genotypes and is seldom recommended currently.[71] These disease-modifying treatments—which include *TTR* gene silencers (ribonucleic acid interference [RNAi] therapeutics patisiran[28] and vutrisiran;[30] antisense oligonucleotides [ASO] inotersen[29] and eplontersen) and TTR stabilizers (tafamidis, diflunisal)—have shown clinical benefit through improving multisystem manifestations in patients with ATTRv amyloidosis.[60,61,72–80] Of these, tafamidis, is approved in Europe but not in the US for the treatment of patients with polyneuropathy. Figure 3 illustrates the mode of action of the different classes of disease-modifying therapies for the treatment of ATTRv amyloidosis.

### 5.1 | Treatment recommendations and considerations

Based on the available efficacy data, indicating a benefit in both early-stage and more advanced ATTRv amyloidosis with polyneuropathy, we recommend the use of a *TTR* gene silencer therapeutic as a first-line treatment in the US for patients with ATTRv amyloidosis with polyneuropathy.

Outside of *TTR* gene silencers, the generic nonsteroidal anti-inflammatory drug diflunisal has been shown to have TTR-stabilizing properties and has been used off-label for the initial treatment of patients with mild neuropathy symptoms. In our experience, patients can remain stable on diflunisal for several years, but they should be monitored closely for disease progression or possible side effects, including gastroesophageal reflux disease or kidney disease. Once disease progression is observed, we recommend switching to a gene silencer therapy.

Recommendations on choice of a specific treatment are hindered by the lack of head-to-head studies of the agents described above, and the lack of a direct comparison of the pivotal trials.[81] However, based on the efficacy data published, all gene-silencing agents are recommended as appropriate treatments for patients with ATTRv amyloidosis with polyneuropathy.

Although not approved for treatment of polyneuropathy in the US, tafamidis is approved for treatment of ATTRv amyloidosis with neurologic involvement in Europe and Latin America based on the evidence of efficacy in patients with early-stage Val30Met disease.[74,82] In the US, tafamidis is approved only for the treatment of patients with TTR amyloid cardiomyopathy.[83]

Clinicians should consider the efficacy and safety considerations when prescribing a particular disease-modifying therapy, in addition to any comorbidities and personal preferences around ease of use for the individual patient. For example, the Risk Evaluation and Mitigation Strategy weekly monitoring required for inotersen may be inconvenient for some patients, who may instead find the use of vutrisiran or eplontersen more attractive, which offers the same convenience of subcutaneous delivery but without the additional safety concerns. Alternatively, younger patients with no other health-related issues (kidney or thrombosis) may choose inotersen over patisiran for the convenience of the subcutaneous administration.

Prior liver transplantation may also be an influencing factor for disease-modifying treatment choice. Patients who experience neuropathy progression post-liver transplantation may benefit from treatment with gene silencers.[84,85] In a Phase 3b study of 23 patients with ATTRv amyloidosis with polyneuropathy progression post-liver transplantation, patisiran demonstrated a positive benefit:risk profile and was able to improve neuropathy, quality of life, and autonomic symptoms in these patients who had previously experienced disease worsening. A separate study showed that inotersen treatment could stabilize or improve neuropathy impairment in nine patients who had experienced disease progression post-liver transplantation, although three of the nine assessed patients discontinued inotersen treatment due to thrombocytopenia.[84]

Ultimately, the choice of treatment should be a shared decision between the individual patient and the treating physician, factoring in patient status, drug efficacy and safety, and impact of administration and monitoring on patient lifestyle.

**TABLE 5** Symptom management options for patients with ATTRv amyloidosis with polyneuropathy in the United States.

| Symptoms/ manifestation targeted | Treatment/care management options | Side effects and other considerations for prescribing |
|---|---|---|
| Neuropathic pain | Gabapentin, pregabalin | Sedation, nausea, leg edema |
| | Duloxetine, venlafaxine | Nausea, constipation, dizziness |
| | Paracetamol | |
| | Oxcarbazepine, lamotrigine | Hyponatremia, nausea, vomiting |
| | Nortriptyline, amitriptyline | Constipation, orthostatic hypotension, sedation |
| Diarrhea | Tincture of opioid | Itching, nausea, constipation |
| | Loperamide | Dizziness, drowsiness, nausea, constipation |
| | Eluxadoline | Constipation, nausea, vomiting, abdominal pain, drowsiness |
| | Dicyclomine | Dizziness, dry mouth, nausea, vomiting, constipation |
| Constipation | Senna glycoside | Nausea, stomachache, diarrhea |
| | Docusate | Nausea, stomachache, diarrhea |
| | Metamucil | Nausea, intestinal gas, cramps, mild diarrhea |
| | Pyridostigmine | Stomach pain, nausea, vomiting, diarrhea, muscle cramps, twitching, increased salivation |
| Appetite stimulant | Mirtazapine | Drowsiness, dizziness, confusion, dry mouth, constipation, nausea |
| | Dronabinol | Drowsiness, dizziness, confusion, stomach pain, nausea |
| Erectile dysfunction | Sildenafil | Headache, orthostatic hypotension, visual changes, congested or runny nose |
| | Alprostadil | Hypotension, headache, balanoposthitis |
| Orthostatic hypotension | Midodrine | Supine hypertension, itching, frequent urination |
| | Fludrocortisone | Supine hypertension, swelling, potential to worsen cardiac failure |
| | Droxidopa | Supine hypertension, headache, dizziness, nausea |
| | Pyridostigmine | Stomach pain, nausea, vomiting, diarrhea, muscle cramps, twitching, increased salivation |
| | Atomoxetine | Supine hypertension |
| | Compression stockings and abdominal binder | |
| Gastroparesis | Metoclopramide | Fatigue, dizziness, drowsiness, abnormal movements, headaches |
| | Erythromycin | Upset stomach, nausea, vomiting, loss of appetite, skin rash |
| Nausea, vomiting | Ondansetron | Prolonged QT, diarrhea, constipation, headache, fatigue and drowsiness, agitation |
| Dry eye | Preservative-free artificial tears | |
| | Nighttime mask and eye ointment or nighttime gel | |
| Hand weakness | Occupational therapy | |
| Gait, cervical/lumbar radiculopathy | Physical therapy/strengthening/core exercises | |
| Foot drop | AFO | |
| CTS | Wrist splints/surgical evaluation | |
| Oculoleptomeningeal involvement | No available treatment, although antiepileptic drugs may be used for seizures | Condition is very rare; however, the frequency may increase with prolonged survival; antiepileptic drugs should be used only for proven seizures on electroencephalogram |
| Hydrocephalus for oculoleptomeningeal types | VP shunt placement | |

Abbreviations: AFO, ankle foot orthoses; ATTRv, hereditary transthyretin (v for variant); CTS, carpal tunnel syndrome; QT, QT interval; VP, ventriculoperitoneal.

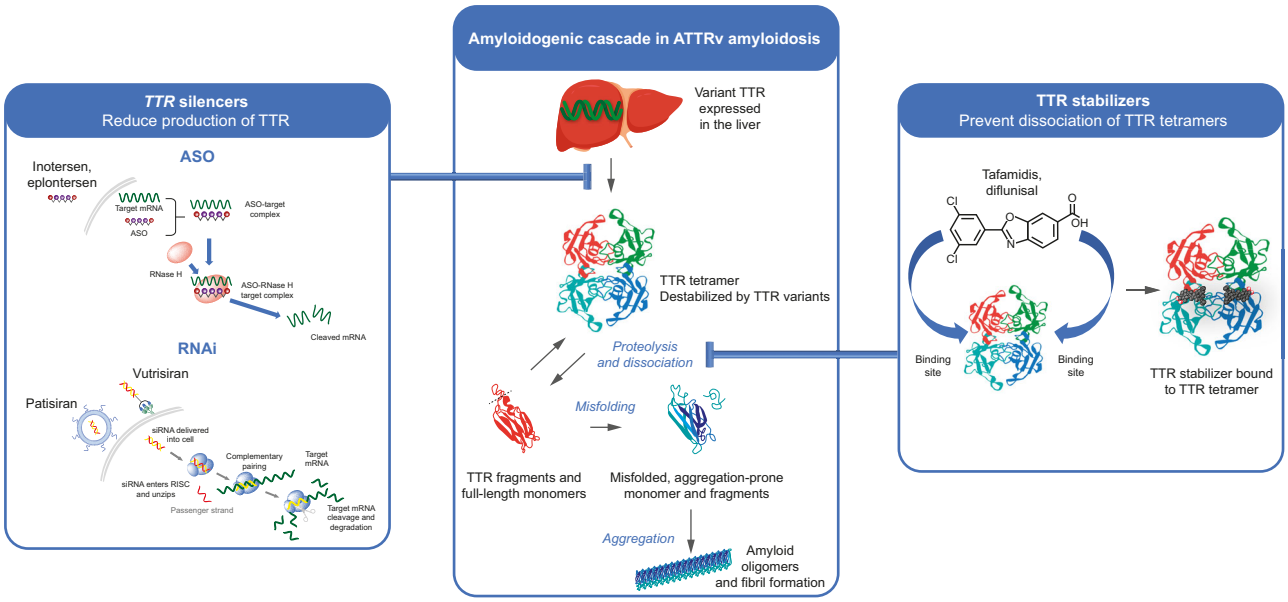


**FIGURE 3** Mode of action of the different classes of disease-modifying therapies for ATTRv amyloidosis. Gene silencer therapeutics inotersen, patisiran, and, more recently, vutrisiran or eplontersen are approved by the FDA for the treatment of ATTRv amyloidosis with polyneuropathy. Patisiran and vutrisiran are RNAi therapeutics that target hepatic production of both variant and wt TTR. Inotersen and eplontersen are ASO therapies designed to reduce levels of both the wt and variant forms of TTR. TTR stabilizers inhibit the misfolding of the TTR protein and subsequent amyloid deposition through binding to and increasing the stability of circulating TTR tetramers and preventing their dissociation to monomers. Although not approved for use in ATTRv amyloidosis, diflunisal—a generic nonsteroidal anti-inflammatory drug—is available for off-label use in the US. Tafamidis—an oral, small-molecule TTR stabilizer—is approved in the US but only for the treatment of the cardiomyopathy of ATTRv amyloidosis. ASO, antisense oligonucleotide; ATTRv, hereditary transthyretin (v for variant); FDA, US Food and Drug Administration; mRNA, messenger ribonucleic acid; RISC, RNA-induced silencing complex; RNAi, ribonucleic acid interference; RNase H, ribonuclease H; siRNA, small interfering ribonucleic acid; TTR, transthyretin; US, United States; wt, wild-type.

## 5.2 | Notable implications regarding treatment choice

### 5.2.1 | Gene silencers for patients with cardiac involvement

Currently, gene silencers are not approved for the treatment of patients with pure cardiac phenotype. However, there were positive results from the APOLLO-B study in patients with either ATTRv or ATTRwt cardiac amyloidosis that demonstrated the benefit of patisiran on functional capacity, quality of life, cardiac biomarkers, and exploratory echocardiographic parameters, compared with placebo.[86] Of note, exploratory endpoint analysis of the NEURO-TTR and HELIOS-A studies demonstrated that inotersen and vutrisiran treatment, respectively, can stabilize or improve several cardiac manifestations in patients with ATTRv amyloidosis with polyneuropathy, indicating a potential benefit overall of RNAi and ASO therapeutics in patients with concurrent cardiomyopathy.[80,87]

### 5.2.2 | Limited evidence for combination therapy

Although the different treatment modalities may be complementary, there is limited evidence for the role of combination therapy. A post hoc analysis showed that patisiran efficacy and safety were similar with or without concomitant TTR stabilizer use, although this combination has not been explored further in clinical studies.[88,89] Similarly, other combinations of approved therapies (with, e.g., doxycycline, tauroursodeoxycholic acid, green tea, and other therapies) have yet to undergo rigorous clinical testing.

### 5.2.3 | Current lack of treatment for central nervous system/ocular symptoms

None of the currently approved or available therapies has been investigated in patients with central nervous system (CNS) or ocular manifestations, and it seems unlikely that the current gene silencer therapies will show efficacy given that they target hepatic TTR synthesis and not choroid plexus TTR production within the CNS. With the emergence of disease-targeting therapies that are prolonging the life span of patients with ATTRv amyloidosis, it is possible that there will be an increase in the number of CNS and ocular manifestations, which typically occur later in the course of the disease;[90] yet, there is currently no evidence for effective treatment of CNS and ocular manifestations using a disease-modifying therapy. However, a small US proof-of-concept study was undertaken in 10 patients treated with tolcapone (NCT03591757), a drug believed to cross the blood–brain barrier

and penetrate the CNS, and thus potentially able to stabilize variant TTR protein in this system. Stabilization of TTR levels following 4 weeks' treatment was shown but could not be correlated with clinical effect due to this short time period. Expansion of this study would allow for further investigation of treatment for this subpopulation.

### 5.2.4 | Advanced disease

The efficacy of disease-modifying treatments has not been well characterized in patients with more advanced disease (FAP Stage 3 or polyneuropathy disability score IV). Although some countries limit the use of these treatments in this patient population, those that are already receiving these medications should not discontinue if their disease progresses to FAP Stage 3. The mode of action of these treatments, to reduce amyloid burden, offers potential benefit to patients with later-stage disease and we still recommend this treatment for this population.

## 6 | LONGER TERM DISEASE MANAGEMENT AND RESPONSE TO TREATMENT

Following initiation of treatment, patients should be monitored at a minimum of every 6 months, depending on the specific patient needs or clinical assessment center. As with initial monitoring of disease progression (Tables 3 and 4), assessments will include a neurologic examination and a focused history to assess for other complications of ATTRv amyloidosis and any potential disease progression. Clinicians may also consider monitoring for development or worsening cardiac manifestations. Of note, clinicians should consider the additional time potentially required (>12 months) to observe any treatment benefit on axonal reinnervation, especially in patients with more advanced disease. There may be some benefit to prealbumin (assessing TTR levels) testing over time, to provide reassurance of pharmacologic response to treatment for some patients, although there is no evidence to recommend modifying therapies based on TTR levels.

As mentioned, while patients receiving diflunisal may benefit from the switch to a *TTR* gene silencer following disease progression, currently there are no clear alternative treatment options if patients have progressed while on gene-silencing therapies. However, before considering possible treatment failures and switching to alternative therapies, clinicians should perform a full and thorough review of symptomatic treatment that a patient may be receiving to avoid confounding disease progression with any nontreated symptoms. For example, weakness reported by a patient may be misinterpreted as neuropathy progression instead of undetected orthostatic hypotension, which could potentially be improved with symptomatic treatment.

Given that untreated ATTRv amyloidosis is a progressive degenerative process and treatment largely stabilizes but does not necessarily reverse existing axonal damage, patients are not expected to continuously improve, and lifelong treatment is required to ameliorate progression. Based on the multisystem involvement of ATTRv amyloidosis and varying symptom severity, it is likely that any improvement will not occur at the same rate for all symptoms. For example, a patient may report far less frequent diarrhea within a short time frame, whereas improvement in neuropathy may not be objectively observed until much later. Therefore, all aspects of the disease—including expected natural history and impact on clinical manifestations and quality of life—should be evaluated before determining the clinical effectiveness of a specific treatment or whether a treatment should be stopped completely.

## 7 | CONCLUSION

ATTRv amyloidosis with polyneuropathy is a progressive disease associated with poor prognosis, such that early disease identification and timely therapeutic intervention are key to achieving better outcomes for patients. We have provided US-specific guidance to help clinicians in the US with diagnosis, progression monitoring, and treatment of patients with ATTRv amyloidosis with polyneuropathy.

Recent years have brought tremendous advances in disease-modifying pharmacotherapeutics, which should be reserved for patients with active disease, in accordance with their approved indication. However, there remains a lack of evidence to support recommendations or consensus in areas that include monitoring and therapeutic intervention in asymptomatic patients, the definition of disease progression and how to treat patients who do not respond to/worsen on current treatments, and management of emerging CNS and ocular disease in longer-surviving patients. Ongoing or planned clinical trials in patients with ATTRv amyloidosis with polyneuropathy remain fundamental to provide robust evidence to support future recommendations in this rapidly evolving field.

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## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed.

## ETHICS STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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## REFERENCES

1. Hanna M. Novel drugs targeting transthyretin amyloidosis. *Curr Heart Fail Rep*. 2014;11:50-57.
2. Mohty D, Damy T, Cosnay P, et al. Cardiac amyloidosis: updates in diagnosis and management. *Arch Cardiovasc Dis*. 2013;106:528-540.
3. Adams D, Coelho T, Obici L, et al. Rapid progression of familial amyloidotic polyneuropathy: a multinational natural history study. *Neurology*. 2015;85:675-682.
4. Hawkins PN, Ando Y, Dispenzeri A, Gonzalez-Duarte A, Adams D, Suhr OB. Evolving landscape in the management of transthyretin amyloidosis. *Ann Med*. 2015;47:625-638.
5. Parman Y, Adams D, Obici L, et al. Sixty years of transthyretin familial amyloid polyneuropathy (TTR-FAP) in Europe: where are we now? A European network approach to defining the epidemiology and management patterns for TTR-FAP. *Curr Opin Neurol*. 2016;29(Suppl 1): S3-S13.
6. Monaco HL, Rizzi M, Coda A. Structure of a complex of two plasma proteins: transthyretin and retinol-binding protein. *Science*. 1995;268: 1039-1041.
7. Koike H, Katsuno M. Ultrastructure in transthyretin amyloidosis: from pathophysiology to therapeutic insights. *Biomedicines*. 2019;7:11.
8. Mangione PP, Verona G, Corazza A, et al. Plasminogen activation triggers transthyretin amyloidogenesis *in vitro*. *J Biol Chem*. 2018;293: 14192-14199.
9. Marcoux J, Mangione PP, Porcari R, et al. A novel mechano-enzymatic cleavage mechanism underlies transthyretin amyloidogenesis. *EMBO Mol Med*. 2015;7:1337-1349.
10. Conceição I, Gonzalez-Duarte A, Obici L, et al. "Red-flag" symptom clusters in transthyretin familial amyloid polyneuropathy. *J Peripher Nerv Syst*. 2016;21:5-9.
11. Shin SC, Robinson-Papp J. Amyloid neuropathies. *Mt Sinai J Med*. 2012;79:733-748.
12. Damy T, Judge DP, Kristen AV, Berthet K, Li H, Aarts J. Cardiac findings and events observed in an open-label clinical trial of tafamidis in patients with non-Val30Met and non-Val122Ile hereditary transthyretin amyloidosis. *J Cardiovasc Transl Res*. 2015;8:117-127.
13. Rapezzi C, Quarta CC, Obici L, et al. Disease profile and differential diagnosis of hereditary transthyretin-related amyloidosis with exclusively cardiac phenotype: an Italian perspective. *Eur Heart J*. 2013;34: 520-528.
14. Coelho T, Maurer MS, Suhr OB. THAOS – The Transthyretin Amyloidosis Outcomes Survey: initial report on clinical manifestations in patients with hereditary and wild-type transthyretin amyloidosis. *Curr Med Res Opin*. 2013;29:63-76.
15. Ando Y, Coelho T, Berk JL, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. *Orphanet J Rare Dis*. 2013;8:31.
16. Mariani LL, Lozeron P, Theaudin M, et al. Genotype-phenotype correlation and course of transthyretin familial amyloid polyneuropathies in France. *Ann Neurol*. 2015;78:901-916.
17. Coelho T, Inês M, Conceição I, Soares M, de Carvalho M, Costa J. Natural history and survival in stage 1 Val30Met transthyretin familial amyloid polyneuropathy. *Neurology*. 2018;91:e1999-e2009.
18. Koike H, Tanaka F, Hashimoto R, et al. Natural history of transthyretin Val30Met familial amyloid polyneuropathy: analysis of late-onset cases from non-endemic areas. *J Neurol Neurosurg Psychiatry*. 2012; 83:152-158.
19. Gonzalez-Duarte A, Conceicao I, Amass L, et al. Impact of non-cardiac clinicopathologic characteristics on survival in transthyretin amyloid polyneuropathy. *Neurol Ther*. 2020;9:135-149.
20. Swiecicki PL, Zhen DB, Mauermann ML, et al. Hereditary ATTR amyloidosis: a single-institution experience with 266 patients. *Amyloid*. 2015;22:123-131.
21. Adams D, Suhr OB, Hund E, et al. First European consensus for diagnosis, management, and treatment of transthyretin familial amyloid polyneuropathy. *Curr Opin Neurol*. 2016;29(suppl 1):S14-S26.
22. Adams D, Theaudin M, Cauquil C, Algalarrondo V, Slama M. FAP neuropathy and emerging treatments. *Curr Neurol Neurosci Rep*. 2014; 14:435.
23. Cruz MW, Schmidt H, Botteman MF, et al. Epidemiological and clinical characteristics of persons with transthyretin hereditary amyloid polyneuropathy: a global synthesis of 532 cases. *Amyloid*. 2017;24: 109-110.
24. Kaku MC, Bhadola S, Berk JL, Sanchorawala V, Connors LH, Lau KHV. Neurological manifestations of hereditary transthyretin amyloidosis: a focus on diagnostic delays. *Amyloid*. 2022;29:1-6.
25. Maurer MS, Bokhari S, Damy T, et al. Expert consensus recommendations for the suspicion and diagnosis of transthyretin cardiac amyloidosis. *Circ Heart Fail*. 2019;12:e006075.
26. Kittleson MM, Maurer MS, Ambardekar AV, et al. Cardiac amyloidosis: evolving diagnosis and management: a scientific statement from the American Heart Association. *Circulation*. 2020;142:e7-e22.
27. Adams D, Ando Y, Beirao JM, et al. Expert consensus recommendations to improve diagnosis of ATTR amyloidosis with polyneuropathy. *J Neurol*. 2021;268:2109-2122.
28. Alnylam Pharmaceuticals Inc. US prescribing information: ONPATTRO (patisiran) lipid complex injection, for intravenous use: Food and Drug Administration. Accessed March 15, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210922s000lbl.pdf
29. Akcea Therapeutics Inc. US prescribing information: TEGSEDI™ (inotersen) injection, for subcutaneous use. Accessed March 15, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/211172lbl.pdf
30. Alnylam Pharmaceuticals Inc. US prescribing information: AMVUTTRA (vutrisiran) injection, for subcutaneous use: Food and Drug Administration. Accessed March 15, 2023. https://www.alnylam.com/sites/default/files/pdfs/amvuttra-us-prescribing-information.pdf
31. Rowczenio DM, Noor I, Gillmore JD, et al. Online registry for mutations in hereditary amyloidosis including nomenclature recommendations. *Hum Mutat*. 2014;35:E2403-E2412.
32. Rowczenio DM, Noor I, Gillmore JD, et al. Mutations in hereditary amyloidosis. 2014. Accessed November 17, 2017. http://www.amyloidosismutations.com/
33. Pinto MV, Pinto LF, Dias M, et al. Late-onset hereditary ATTR V30M amyloidosis with polyneuropathy: characterization of Brazilian subjects from the THAOS registry. *J Neurol Sci*. 2019;403:1-6.
34. Maurer MS, Hanna M, Grogan M, et al. Genotype and phenotype of transthyretin cardiac amyloidosis: THAOS (Transthyretin Amyloid Outcome Survey). *J Am Coll Cardiol*. 2016;68:161-172.

35. Jacobson DR, Alexander AA, Tagoe C, Buxbaum JN. Prevalence of the amyloidogenic transthyretin (TTR) V122I allele in 14 333 African-Americans. *Amyloid*. 2015;22:171-174.
36. Buxbaum JN, Ruberg FL. Transthyretin V122I (pV142I)* cardiac amyloidosis: an age-dependent autosomal dominant cardiomyopathy too common to be overlooked as a cause of significant heart disease in elderly African Americans. *Genet Med*. 2017;19:733-742.
37. Lin X, Yarlas A, Vera-Llonch M, et al. Rate of neuropathic progression in hereditary transthyretin amyloidosis with polyneuropathy and other peripheral neuropathies: a systematic review and meta-analysis. *BMC Neurol*. 2021;21:70.
38. Zampino S, Sheikh FH, Vaishnav J, et al. Phenotypes associated with the Val122Ile, Leu58His, and late-onset Val30Met variants in patients with hereditary transthyretin amyloidosis. *Neurology*. 2023;100: e2036-e2044.
39. Sperry BW, Reyes BA, Ikram A, et al. Tenosynovial and cardiac amyloidosis in patients undergoing carpal tunnel release. *J Am Coll Cardiol*. 2018;72:2040-2050.
40. Verriello L, Dalla Torre C, Pauletto G, Gigli G. Interpreting signals from the peripheral nerve in amyloidosis: a call for action. *Vessel Plus*. 2021;5:51.
41. Karam C, Dimitrova D, Christ M, Heitner SB. Carpal tunnel syndrome and associated symptoms as first manifestation of hATTR amyloidosis. *Neurol Clin Pract*. 2019;9:309-313.
42. Gonzalez-Duarte A. Autonomic involvement in hereditary transthyretin amyloidosis (hATTR amyloidosis). *Clin Auton Res*. 2019;29:245-251.
43. Ruberg FL, Grogan M, Hanna M, Kelly JW, Maurer MS. Transthyretin amyloid cardiomyopathy: JACC state-of-the-art review. *J Am Coll Cardiol*. 2019;73:2872-2891.
44. Hara Y, Tajiri Y, Kawano K, Hoshikawa S, Kita Y. The tenosynovitis of fingers associated with transthyretin amyloidosis. *J Hand Surg Asian Pac*. 2020;25:340-344.
45. Aus dem Siepen F, Hein S, Prestel S, et al. Carpal tunnel syndrome and spinal canal stenosis: harbingers of transthyretin amyloid cardiomyopathy? *Clin Res Cardiol*. 2019;108:1324-1330.
46. Karam C, Dimitrova D, Heitner SB. Misdiagnosis of hATTR amyloidosis: a single US site experience. *Amyloid*. 2020;27:69-70.
47. Plante-Bordeneuve V, Ferreira A, Lalu T, et al. Diagnostic pitfalls in sporadic transthyretin familial amyloid polyneuropathy (TTR-FAP). *Neurology*. 2007;69:693-698.
48. Lozeron P, Mariani LL, Dodet P, et al. Transthyretin amyloid polyneuropathies mimicking a demyelinating polyneuropathy. *Neurology*. 2018;91:e143-e152.
49. Vogt B, Chahin N, Wiszniewski W, Ragole T, Karam C. Screening for genetic mutations in patients with neuropathy without definite etiology is useful. *J Neurol*. 2020;267:2648-2654.
50. Dyck PJ, Oviatt KF, Lambert EH. Intensive evaluation of referred unclassified neuropathies yields improved diagnosis. *Ann Neurol*. 1981;10:222-226.
51. Ebenezer GJ, Liu Y, Judge DP, et al. Cutaneous nerve biomarkers in transthyretin familial amyloid polyneuropathy. *Ann Neurol*. 2017;82: 44-56.
52. Luigetti M, Conte A, Del Grande A, et al. TTR-related amyloid neuropathy: clinical, electrophysiological and pathological findings in 15 unrelated patients. *Neurol Sci*. 2013;34:1057-1063.
53. van Gameren I, Hazenberg BP, Bijzet J, van Rijswijk MH. Diagnostic accuracy of subcutaneous abdominal fat tissue aspiration for detecting systemic amyloidosis and its utility in clinical practice. *Arthritis Rheum*. 2006;54:2015-2021.
54. Paulsson Rokke H, Sadat Gousheh N, Westermark P, et al. Abdominal fat pad biopsies exhibit good diagnostic accuracy in patients with suspected transthyretin amyloidosis. *Orphanet J Rare Dis*. 2020;15:278.
55. Bokhari S, Castano A, Pozniakoff T, et al. $^{99m}$Tc-pyrophosphate scintigraphy for differentiating light-chain cardiac amyloidosis from the transthyretin-related familial and senile cardiac amyloidoses. *Circ Cardiovasc Imaging*. 2013;6:195-201.
56. Gillmore JD, Maurer MS, Falk RH, et al. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. *Circulation*. 2016;133:2404-2412.
57. Dorbala S, Ando Y, Bokhari S, et al. ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI expert consensus recommendations for multimodality imaging in cardiac amyloidosis: part 2 of 2-diagnostic criteria and appropriate utilization. *J Nucl Cardiol*. 2019;25:854-865.
58. Conceição I, Damy T, Romero M, et al. Early diagnosis of ATTR amyloidosis through targeted follow-up of identified carriers of TTR gene mutations. *Amyloid*. 2019;26:3-9.
59. Adams D, Beaudonnet G, Adam C, et al. Familial amyloid polyneuropathy: when does it stop to be asymptomatic and need a treatment? *Rev Neurol (Paris)*. 2016;172:645-652.
60. Adams D, Polydefkis M, González-Duarte A, et al. Long-term safety and efficacy of patisiran for hereditary transthyretin-mediated amyloidosis with polyneuropathy: 12-month results of an open-label extension study. *Lancet Neurol*. 2021;20:49-59.
61. Brannagan TH, Wang AK, Coelho T, et al. Early data on long-term efficacy and safety of inotersen in patients with hereditary transthyretin amyloidosis: a 2-year update from the open-label extension of the NEURO-TTR trial. *Eur J Neurol*. 2020;27:1374-1381.
62. Ticau S, Sridharan GV, Tsour S, et al. Neurofilament light chain as a biomarker of hereditary transthyretin-mediated amyloidosis. *Neurology*. 2021;96:e412-e422.
63. Louwsma J, Brunger AF, Bijzet J, et al. Neurofilament light chain, a biomarker for polyneuropathy in systemic amyloidosis. *Amyloid*. 2021;28:50-55.
64. Luigetti M, Di Paolantonio A, Guglielmino V, et al. Neurofilament light chain as a disease severity biomarker in ATTRv: data from a single-Centre experience. *Neurol Sci*. 2022;43:2845-2848.
65. Adams D. Recent advances in the treatment of familial amyloid polyneuropathy. *Ther Adv Neurol Disord*. 2013;6:129-139.
66. Coutinho P, DeSilva AM, Lima JL, Barbosa AR. Forty years of experience with type I amyloid neuropathy: review of 483 cases. In: Glenner G, Costa P, de Freitas A, eds. *Amyloid and Amyloidosis*. Excerpta Medica; 1980:88-98.
67. Dungu JN, Anderson LJ, Whelan CJ, Hawkins PN. Cardiac transthyretin amyloidosis. *Heart*. 2012;98:1546-1554.
68. Vinik EJ, Vinik AI, Paulson JF, et al. Norfolk QOL-DN: validation of a patient reported outcome measure in transthyretin familial amyloid polyneuropathy. *J Peripher Nerv Syst*. 2014;19:104-114.
69. van Nes SI, Vanhoutte EK, van Doorn PA, et al. Rasch-built Overall Disability Scale (R-ODS) for immune-mediated peripheral neuropathies. *Neurology*. 2011;76:337-345.
70. Sletten DM, Suarez GA, Low PA, Mandrekar J, Singer W. COMPASS 31: a refined and abbreviated composite autonomic symptom score. *Mayo Clin Proc*. 2012;87:1196-1201.
71. Ericzon BG, Wilczek HE, Larsson M, et al. Liver transplantation for hereditary transthyretin amyloidosis: after 20 years still the best therapeutic alternative? *Transplantation*. 2015;99:1847-1854.
72. Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. *N Engl J Med*. 2018;379:11-21.
73. Benson MD, Waddington-Cruz M, Berk JL, et al. Inotersen treatment for patients with hereditary transthyretin amyloidosis. *N Engl J Med*. 2018;379:22-31.
74. Coelho T, Maia LF, Martins da Silva A, et al. Tafamidis for transthyretin familial amyloid polyneuropathy: a randomized, controlled trial. *Neurology*. 2012;79:785-792.
75. Obici L, Berk JL, González-Duarte A, et al. Quality of life outcomes in APOLLO, the phase 3 trial of the RNAi therapeutic patisiran in patients with hereditary transthyretin-mediated amyloidosis. *Amyloid*. 2020;27:153-162.

76. González-Duarte A, Berk JL, Quan D, et al. Analysis of autonomic outcomes in APOLLO, a phase III trial of the RNAi therapeutic patisiran in patients with hereditary transthyretin-mediated amyloidosis. *J Neurol*. 2020;267:703-712.
77. Berk JL, Suhr OB, Obici L, et al. Repurposing diflunisal for familial amyloid polyneuropathy: a randomized clinical trial. *JAMA*. 2013;310:2658-2667.
78. Brannagan TH, Coelho T, Wang AK, et al. Long-term efficacy and safety of inotersen for hereditary transthyretin amyloidosis: NEURO-TTR open-label extension 3-year update. *J Neurol*. 2022;269:6416-6427.
79. Coelho T, Waddington Cruz M, Chao CC, et al. Characteristics of patients with hereditary transthyretin amyloidosis-polyneuropathy (ATTRv-PN) in NEURO-TTRansform, an open-label phase 3 study of eplontersen. *Neurol Ther*. 2023;12:267-287.
80. Adams D, Tournev IL, Taylor MS, et al. Efficacy and safety of vutrisiran for patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy: a randomized clinical trial. *Amyloid*. 2023;30:1-9.
81. Gonzalez-Duarte A. Novel treatments for hereditary ATTRv amyloidosis. *JAMA*. 2023;330:1433-1434. doi:10.1001/jama.2023.15087
82. European Medicines Agency. Summary of product characteristics: Vyndaqel 20 mg soft capsules. Accessed December 15, 2022. https://www.ema.europa.eu/en/documents/product-information/vyndaqel-epar-product-information_en.pdf
83. Pfizer. US prescribing information: VYNDAQEL® (tafamidis meglumine) capsules, for oral administration and VYNDAMAX™ (tafamidis) capsules, for oral administration. Accessed December 15, 2022. https://www.fda.gov/media/126283/download
84. Moshe-Lilie O, Dimitrova D, Heitner SB, et al. TTR gene silencing therapy in post liver transplant hereditary ATTR amyloidosis patients. *Amyloid*. 2020;27:250-253.
85. Schmidt HH, Wixner J, Plante-Bordeneuve V, et al. Patisiran treatment in patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy after liver transplantation. *Am J Transplant*. 2022;22:1646-1657.
86. Maurer MS, Fontana M, Berk JL, et al. Primary results from APOLLO-B, a phase 3 study of patisiran in patients with transthyretin-mediated amyloidosis with cardiomyopathy. Heart Failure Society of America Annual Scientific Meeting, Heidelberg, Germany. Oral presentation 2022.
87. Dasgupta NR, Rissing SM, Smith J, Jung J, Benson MD. Inotersen therapy of transthyretin amyloid cardiomyopathy. *Amyloid*. 2020;27:52-58.
88. Lin H, Merkel M, Hale C, Marantz JL. Experience of patisiran with transthyretin stabilizers in patients with hereditary transthyretin-mediated amyloidosis. *Neurodegener Dis Manag*. 2020;10:289-300.
89. Coelho T, Adams D, Conceição I, et al. A phase II, open-label, extension study of long-term patisiran treatment in patients with hereditary transthyretin-mediated (hATTR) amyloidosis. *Orphanet J Rare Dis*. 2020;15:179.
90. Dohrn MF, Medina J, Olaciregui Dague KR, Hund E. Are we creating a new phenotype? Physiological barriers and ethical considerations in the treatment of hereditary transthyretin-amyloidosis. *Neurol Res Pract*. 2021;3:57.
91. Kittleson MM, Ruberg FL, Ambardekar AV, et al. 2023 ACC expert consensus decision pathway on comprehensive multidisciplinary care for the patient with cardiac amyloidosis. *J Am Coll Cardiol*. 2023;81:1076-1126.
92. Keppel SC, Brannagan TH 3rd, Helmke S, et al. Early-onset of transthyretin amyloidosis in a young Afro-Caribbean woman with Thr60Ala mutation. *JACC Case Rep*. 2020;2:2063-2067.


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