Diagnosis and Treatment of Hereditary Transthyretin Amyloidosis with Polyneuropathy in the United States: Recommendations from a Panel of Experts

Chafic Karam, Michelle L. Mauermann, Alejandra Gonzalez-Duarte, Michelle C. Kaku, Senda Ajroud-Driss, Thomas H. Brannigan III, Michael Polydefkis. *Muscle & Nerve*. 2024; 1–15.doi:10.1002/mus.28026

Interactive Summary

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Diagnosis and Treatment of ATTRv Amyloidosis with Polyneuropathy in the US: Recommendations from a Panel of Experts

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Overview

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Manuscript and Interactive Summary funded by Alnylam® Pharmaceuticals (Cambridge, Massachusetts)

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Overview: Symptoms and Clinical Presentation of ATTRv Amyloidosis with Polyneuropathy

- Genetic heterogeneity in the US → difficult to define a "typical presentation"
  - Possible neurologic and non-neurologic signs and symptoms
- Most important **red flags** for suspicion of ATTRv amyloidosis include:
  - **Rapid neurologic progression** (NIS: ~+12 points/year)
  - Accompanying or prior history of **comorbidities** (i.e., prior or concurrent CTS, autonomic failure, GI dysmotility, and HFpEF)
- 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

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Overview: Making a Diagnosis

Early diagnosis and **treatment initiation** are critical to prevent organ damage that may **be irreversible**

Non-specific neurologic symptoms are often **misdiagnosed** leading to **diagnostic delays**

Key considerations and recommended assessments for diagnosis of ATTRv amyloidosis with polyneuropathy include:

- **Genetic testing** to confirm a diagnosis and exclude other conditions
- **Tissue biopsy** to confirm TTR amyloid deposition in patients with TTR variants but with confounding causes of polyneuropathy
- **Monitoring of pre-symptomatic TTR variant** carriers ~5–10 years ahead of predicted age of onset and follow-up every ~1–2 years

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Overview: Treatment Initiation Timing and Disease Monitoring

Early intervention with disease-modifying treatment results in **better patient outcomes** → Initiate treatment or therapy **as soon as possible** after diagnosis

Disease progression should be **monitored** using recommended assessments (**Table 3** and **Table 4**)

A neurologic assessment along with a detailed **neurologic examination** are recommended **every 6–12 months**

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Overview: Treatment Choice for ATTRv Amyloidosis with Polyneuropathy in the US

TTR gene silencers (patisiran, vutrisiran, inotersen, eplontersen) are recommended as **first-line treatment** for US patients with ATTRv amyloidosis with polyneuropathy[a]

Choice of disease-modifying therapy should take into consideration:

- **Efficacy**
- **Safety** (thrombocytopenia or glomerulonephritis; REMS monitoring required with inotersen[1])
- **Comorbidities**
- **Preference for ease of use** (subcutaneous vs intravenous; dosing frequency)

Choice of treatment should be a **shared decision** between the individual patient and the treating clinician

[a]*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.*

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Overview: Longer-Term Disease Management and Response to Treatment

Patients should be **monitored** (**Table 3** **and Table 4**) at a minimum of **every 6 months** following treatment initiation for worsening of or appearance of **new neurologic or cardiac symptoms**

Patients who initially receive the TTR stabilizer, diflunisal, for the off-label treatment of polyneuropathy but later exhibit **disease progression** may benefit from **switching** to a **TTR gene silencer**

There is currently no clear alternative treatment option if patients exhibit disease progression on TTR gene silencers

All aspects of the disease should be considered **before a decision to change or stop treatment is reached**

(e.g., weakness may be misinterpreted as neuropathy progression instead of undetected orthostatic hypotension or different symptoms of varying severity where any improvement noted may not happen at the same rate)

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Appendix

Purpose and Methodology

- A panel of seven neurologists with expertise in ATTRv amyloidosis in the US reviewed and discussed the pooled responses from a pre-meeting questionnaire
- This questionnaire was developed by Adelphi Communications Ltd, independently of the sponsor Alnylam Pharmaceuticals, following a literature review of expert recommendation articles, natural history studies, clinical trials outcome data, and non-US management guidelines in ATTRv amyloidosis with polyneuropathy
- These 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
- Manuscript and Interactive Summary funded by Alnylam® Pharmaceuticals (Cambridge, Massachusetts)

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Table 1. Possible neurologic manifestations of ATTRv amyloidosis

Symptoms of neuropathy		
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	Light headedness/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)*
	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

*GI manifestations in ATTRv amyloidosis can also be of non-autonomic origin, with deposition of amyloid within the GI system resulting in symptoms such as abdominal pain, esophageal reflux, nausea, constipation, and early satiety.
Adapted from source.

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Table 1. Possible non-neurologic manifestations of ATTRv amyloidosis

Sign/symptoms from other organs/body systems			
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	

Adapted from source.

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Red flag signs/symptoms and prior medical history raising suspicion of ATTRv amyloidosis in patients presenting with symptoms of neuropathy

- Rapid rate of polyneuropathy progression
- Early autonomic dysfunction
  - Erectile dysfunction
  - Lightheadedness from postural hypotension
  - Changes in bowel movements and GI symptoms (often dismissed or misdiagnosed as IBS)
- Bilateral CTS and/or prior surgery for CTS
  - Recurring after release surgery
  - Present in other family members
- Accompanying or prior history of symptoms from other systems (Table 1 →)
  - Cardiac: shortness of breath, arrhythmias, CHF with preserved EF, features of hypertrophic cardiomyopathy
  - Musculoskeletal: rotator cuff, biceps tendon
  - Ophthalmologic: vitreous opacities, periorbital hemorrhages
  - Renal: renal failure and proteinuria
  - GI: unexplained/unintentional weight loss, constipation, diarrhea
- Motor weakness
  - Predominant or early in the course of neuropathy
- Family history of ATTRv amyloidosis
- Prior family history of unexplained:
  - Rapidly progressing polyneuropathy of unknown cause
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  - Sudden cardiac death
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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 • Idiopathic neuropathy • Alcohol neuropathy	• Mild diabetes with severe neuropathy • Weakness with sensory abnormalities; rapid progression • Concurrent development of other symptoms (erectile dysfunction, change in bowel habits); history of other conditions (e.g., unexplained weight loss)	• Concurrent cardiac disease • Nerve biopsy findings • Early motor involvement • Previous or concurrent CTS • Concurrent cardiac history: CHF, arrhythmia, syncope
Demyelinating neuropathy	• CIDP	• Primarily axonal polyneuropathy; no or poor response to prior immunotherapy; accompanying autonomic symptoms • Family history, or other amyloid complication	
Motor neuropathy	• Motor neuron disease/ALS • CIDP	• Concurrent sensory component	• Other organ involvement • Prominent sensory symptoms distinguish from ALS
Small-fiber neuropathy	• Fibromyalgia • Idiopathic small-fiber neuropathy	• Other associated features of ATTRv amyloidosis • 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 • Presence of other complications (e.g., HF)	• Concurrent idiopathic neuropathy or autonomic dysfunction • Trigger finger, lumbar stenosis • Recurrent CTS
Unexpected weight loss	• Malignancy or autoimmune disease	• Other associated features of ATTRv amyloidosis	

Adapted from source.

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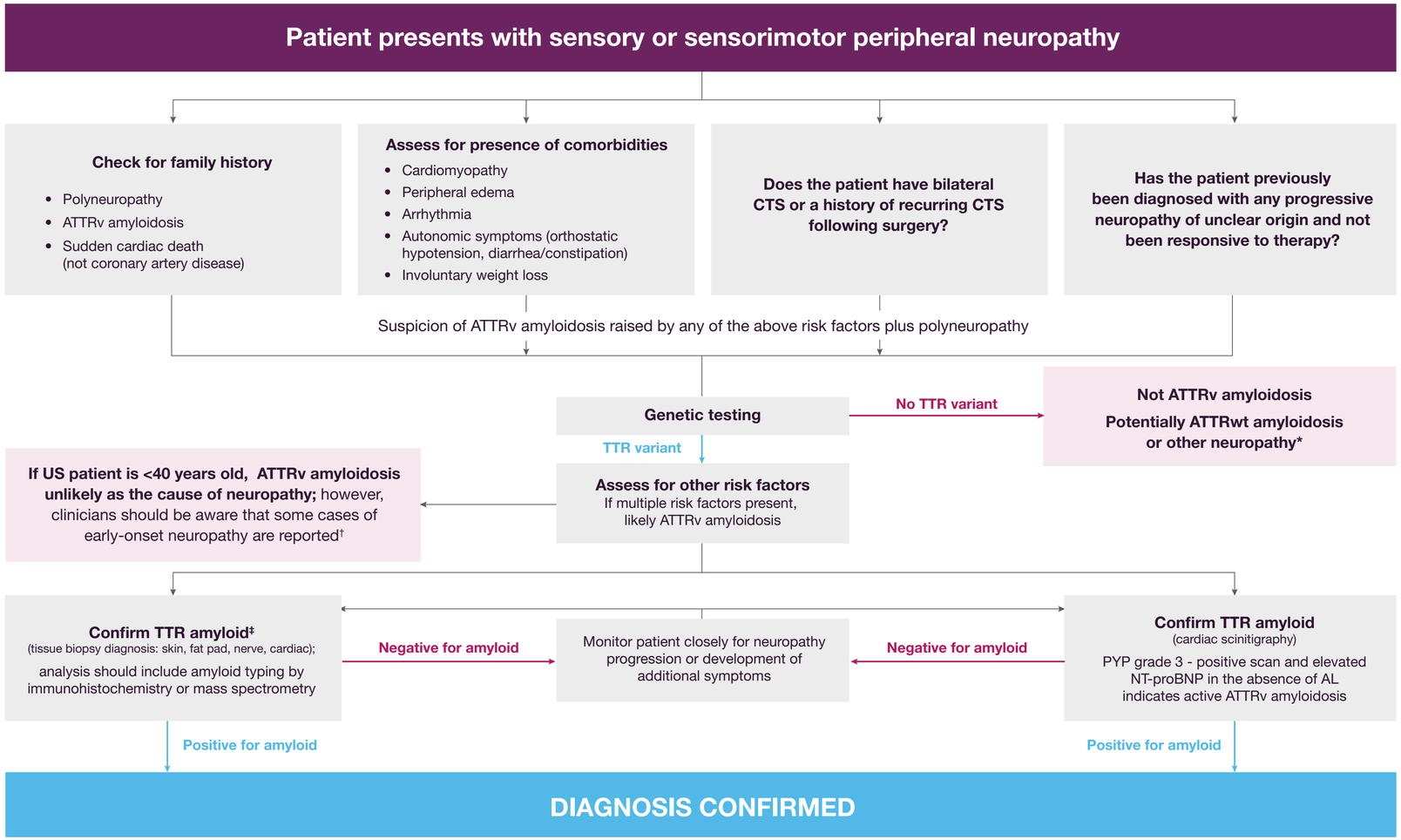

*Patients may be assessed for genetic conditions including Charcot–Marie–Tooth disease and hereditary neuropathy with liability to pressure palsies, or screened for vitamin B12 deficiency, diabetes (hemoglobin A1C assessment), thyroid dysfunction, monoclonal gammopathy (immunofixation electrophoresis), or AL amyloidosis (immunoglobulin free light chain assessment).
†Early onset of polyneuropathy has been reported in ATTRv amyloidosis.[19]
‡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.
Adapted from source.

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Table 3. Recommended assessments/tools for staging or monitoring disease in patients with symptomatic or pre-symptomatic ATTRv amyloidosis

List of assessments for 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 pre-symptomatic variant carriers. Some centers perform only if new symptoms indicative of radiculopathy or CTS, following initial diagnosis. 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. Most centers perform only for clinical trials
Norfolk QOL-DN questionnaire	IIb	1	Annual/every 6 months by those that use in clinical practice. Most centers perform only for clinical trials
COMPASS-31 questionnaire	IIa	2	Annual/every 6 months by those that use in clinical practice. 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

[a]Class I=strong; Class IIa=moderate; Class IIb=weak.
[b]1=very sensitive; 2=sensitive; 3=moderately sensitive.
Adapted from source.

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Table 4. Recommended assessments/tools for staging or monitoring disease in patients with symptomatic or pre-symptomatic ATTRv amyloidosis

List of assessments for non-neurologic symptoms[a]			
Assessment tool	**Strength of recommendation[b]**	**Sensitivity to disease progression (1–3)[c]**	**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

[a]Clinicians should consider a collaborative multispecialty approach to assessment of non-neurologic symptoms to capture the multisystem nature of this disease.[26]
[b]Class I=strong; Class IIa=moderate; Class IIb=weak.
[c]1=very sensitive; 2=sensitive; 3=moderately sensitive.
[d]In patients receiving TTR silencers, prealbumin testing to monitor TTR suppression may provide some reassurance of pharmacologic response to treatment for some patients.
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- Prealbumin[d]	IIa	N/A	At baseline and annually to monitor response to treatment
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Adapted from source.

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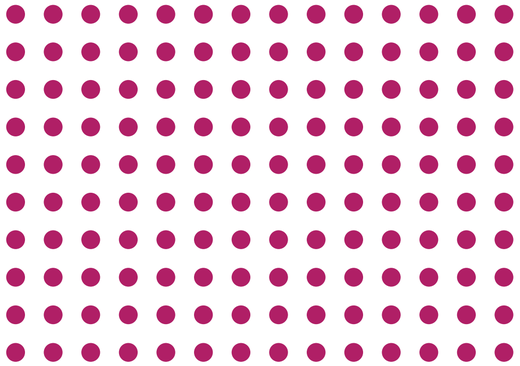
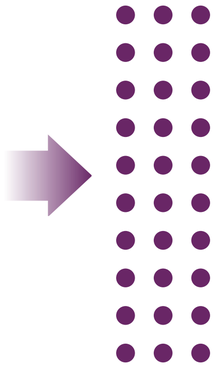
Symptoms and Clinical Presentation of ATTRv Amyloidosis with Polyneuropathy

There are

>140

pathogenic TTR variants, most of which are associated with a **mixed phenotype**[2–6]





>30

TTR variants reported in the US[7]

There are **no specific signs or symptoms of polyneuropathy unique to ATTRv amyloidosis;** a consequence of the genetic heterogeneity observed in the US is that it is **difficult to define a "typical presentation"**

Suspicion of ATTRv amyloidosis should be considered in the context of additional red flags of **accompanying symptoms, other medical conditions, prior medical history, and family history**

Possible **neurologic signs and symptoms** and other **organ manifestations (non-neurologic)** observed in patients with ATTRv amyloidosis are shown in **Table 1**

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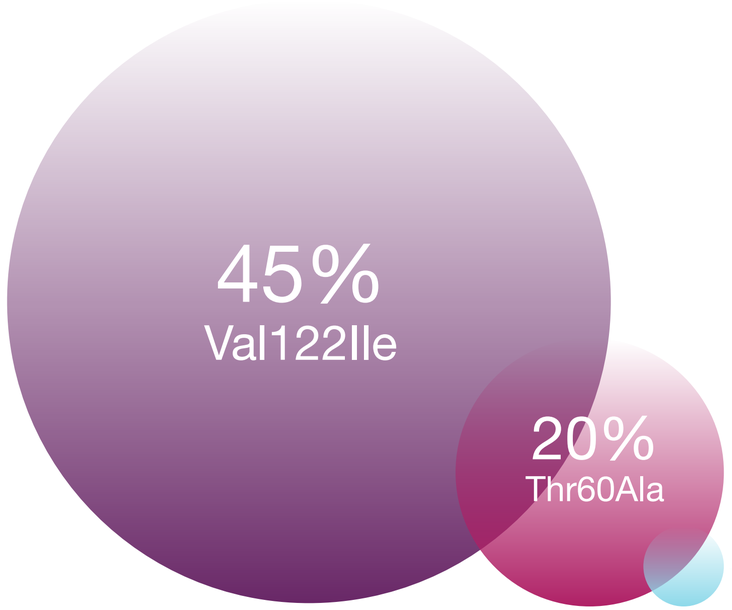
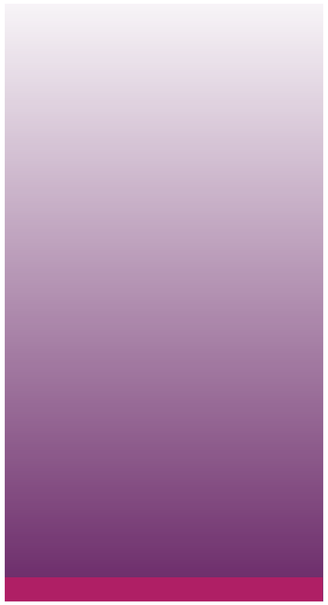


are the most common variants in the **US**[7]



V122I is reported in **3–4%** of Black Americans[8,9]

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Table 1. Possible neurologic manifestations of ATTRv amyloidosis

Symptoms of neuropathy		
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	Light headedness/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)*
	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

*GI manifestations in ATTRv amyloidosis can also be of non-autonomic origin, with deposition of amyloid within the GI system resulting in symptoms such as abdominal pain, esophageal reflux, nausea, constipation, and early satiety.
Adapted from source.

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Table 1. Possible non-neurologic manifestations of ATTRv amyloidosis

Sign/symptoms from other organs/body systems			
Cardiac	**Musculoskeletal**	**Ophthalmologic**	**Renal**
Features of hypertrophic cardiomyopathy	CTS most often bilateral	Vitreous opacities	Renal failure
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Arrhythmia	Rotator cuff injury	Dry eyes	Hematuria
Peripheral edema	Lumbar stenosis	Abnormal conjunctival vessels	
Shortness of breath	Tendon rupture	Cataracts	

Adapted from source.

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Red flags for raising suspicion of ATTRv amyloidosis

The most important red flags for raising suspicion of ATTRv amyloidosis were **rapid neurologic progression** and **accompanying comorbidities** (i.e., concurrent or prior **CTS** **autonomic failure** **GI dysmotility, and HFpEF**)

A **detailed review of medical history** is advised in patients **presenting with CTS**, especially in those patients with no known family history of ATTRv amyloidosis

Autonomic dysfunction can be one of the **earliest manifestations in patients with ATTRv amyloidosis**, often preceding development of overt neurologic symptoms[10]

In addition to CTS, other musculoskeletal manifestations are common in ATTRv and ATTRwt amyloidosis

A full list of red flags for raising suspicion of ATTRv amyloidosis can be found in **Figure 1**

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Patients with ATTRv amyloidosis typically experience worsening of

~+12

points/year in NIS[11]

A notable exception is people with Val122Ile variants, who typically have a mild neuropathy[12]

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CTS is often **bilateral, more refractory to common treatments for CTS, and more prone to recurrence** after CTS release in patients with ATTRv amyloidosis than in patients with idiopathic CTS[13,14]

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Autonomic symptoms are often missed if not specifically queried or can be dismissed as inconsequential

(intermittent GI symptoms of recurrent diarrhea diagnosed as IBS)

or a typical age-related event (erectile dysfunction)

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Red flag signs/symptoms and prior medical history raising suspicion of ATTRv amyloidosis in patients presenting with symptoms of neuropathy

- Rapid rate of polyneuropathy progression
- Early autonomic dysfunction
  - Erectile dysfunction
  - Lightheadedness from postural hypotension
  - Changes in bowel movements and GI symptoms (often dismissed or misdiagnosed as IBS)
- Bilateral CTS and/or prior surgery for CTS
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- Accompanying or prior history of symptoms from other systems (Table 1 →)
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In **endemic regions,** a **family history** of ATTRv amyloidosis **may be prevalent**

In regions with a **heterogeneous population, such as the US,** ATTRv may occur **sporadically** with an **atypical disease, making diagnosis challenging**

A full detailed review of **prior medical** and **family history** **may support diagnosis** in patients with **neurologic symptoms**

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

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Symptoms that precede neuropathy may include:

- Bilateral CTS
- Unintentional weight loss
- GI symptoms
- Vitreous opacities

CTS may precede the onset of neurologic symptoms by between

7–10 years[14,15]

Long-standing idiopathic peripheral neuropathy that **does not respond** to specific treatments for other neuropathies should raise suspicion of ATTRv amyloidosis

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Family history of unexplained:

- Rapidly progressing idiopathic polyneuropathy, particularly occurring in young patients
- HFpEF
- Sudden cardiac death
- Cardiac arrhythmia

→ in patients presenting with neurologic symptoms should raise suspicion

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Red flag signs/symptoms and prior medical history raising suspicion of ATTRv amyloidosis in patients presenting with symptoms of neuropathy

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Table 1. Possible neurologic manifestations of ATTRv amyloidosis

Symptoms of neuropathy		
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	Light headedness/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)*
	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

*GI manifestations in ATTRv amyloidosis can also be of non-autonomic origin, with deposition of amyloid within the GI system resulting in symptoms such as abdominal pain, esophageal reflux, nausea, constipation, and early satiety.
Adapted from source.

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Table 1. Possible non-neurologic manifestations of ATTRv amyloidosis

Sign/symptoms from other organs/body systems			
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	

Adapted from source.

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Making a Diagnosis of ATTRv Amyloidosis with Polyneuropathy

Early diagnosis and treatment of ATTRv amyloidosis are **critical to prevent organ damage** that can be irreversible

Non-specific neurologic symptoms are often **misdiagnosed** as other conditions (e.g., CIDP, diabetic neuropathy; **Table 2**)[16–18]

Key considerations and recommended assessments for diagnosis of ATTRv amyloidosis with polyneuropathy can be found in **Figure 2**

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 • Idiopathic neuropathy • Alcohol neuropathy	• Mild diabetes with severe neuropathy • Weakness with sensory abnormalities; rapid progression • Concurrent development of other symptoms (erectile dysfunction, change in bowel habits); history of other conditions (e.g., unexplained weight loss)	• Concurrent cardiac disease • Nerve biopsy findings • Early motor involvement • Previous or concurrent CTS • Concurrent cardiac history: CHF, arrhythmia, syncope
Demyelinating neuropathy	• CIDP	• Primarily axonal polyneuropathy; no or poor response to prior immunotherapy; accompanying autonomic symptoms • Family history, or other amyloid complication	
Motor neuropathy	• Motor neuron disease/ALS • CIDP	• Concurrent sensory component	• Other organ involvement • Prominent sensory symptoms distinguish from ALS
Small-fiber neuropathy	• Fibromyalgia • Idiopathic small-fiber neuropathy	• Other associated features of ATTRv amyloidosis • 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 • Presence of other complications (e.g., HF)	• Concurrent idiopathic neuropathy or autonomic dysfunction • Trigger finger, lumbar stenosis • Recurrent CTS
Unexpected weight loss	• Malignancy or autoimmune disease	• Other associated features of ATTRv amyloidosis	

Adapted from source.

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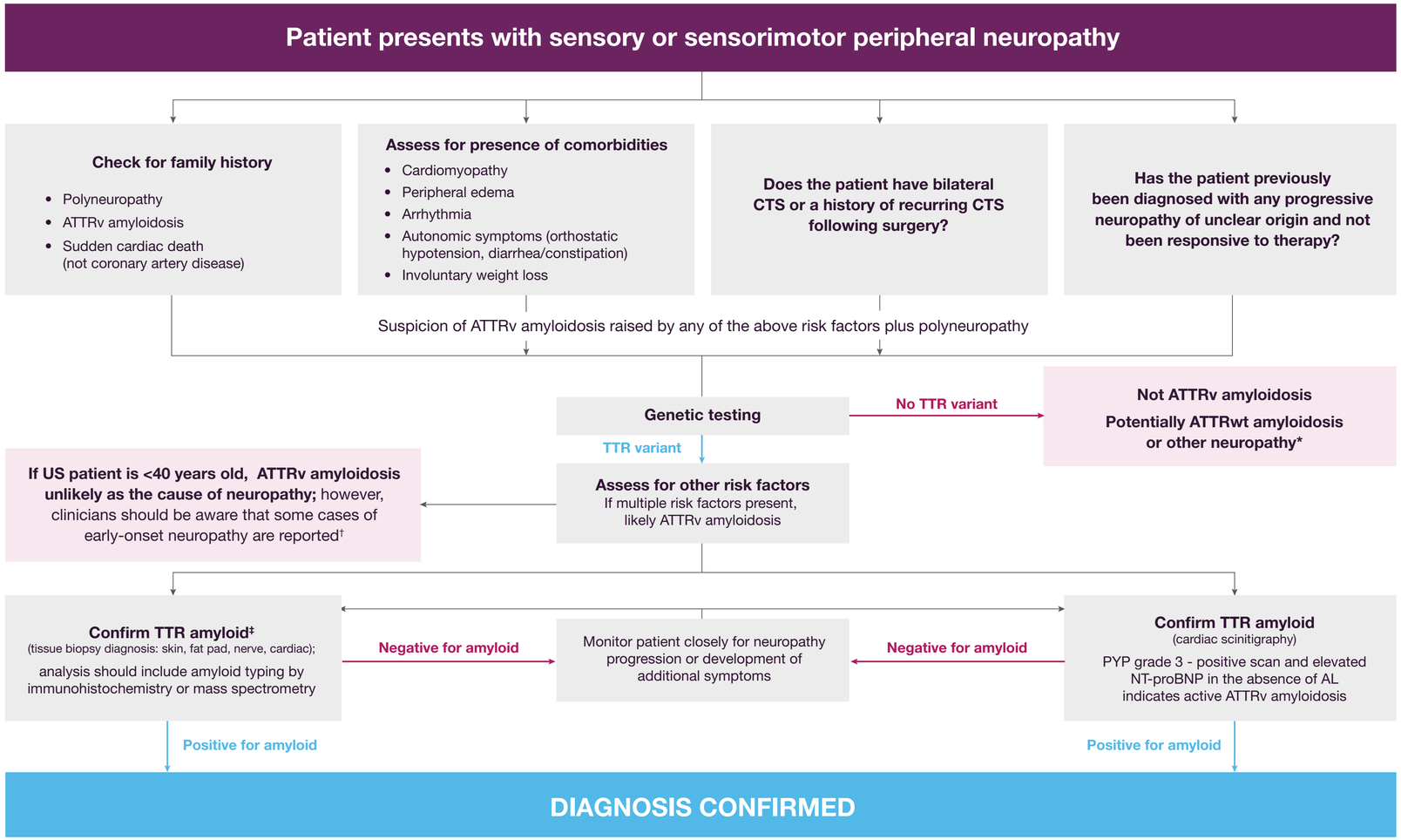

*Patients may be assessed for genetic conditions including Charcot–Marie–Tooth disease and hereditary neuropathy with liability to pressure palsies, or screened for vitamin B12 deficiency, diabetes (hemoglobin A1C assessment), thyroid dysfunction, monoclonal gammopathy (immunofixation electrophoresis), or AL amyloidosis (immunoglobulin free light chain assessment).
†Early onset of polyneuropathy has been reported in ATTRv amyloidosis.[19]
‡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.
Adapted from source.

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Genetic and Laboratory Testing

Genetic testing/panel screening is a **key tool** for **confirming diagnosis** and **differentiating** ATTRv amyloidosis from other conditions

In patients with **unexplained progressive peripheral neuropathy, testing** for a panel of genes and/or laboratory screening is **useful to exclude other causes** of neuropathies[20,21]

Contents

Genetic counseling should occur before genetic testing of an individual suspected of having ATTRv amyloidosis

If a TTR variant is identified, counseling should be extended to the individual's at-risk family members

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Tissue Biopsy

In the US, due to **variable presentation and less penetrant TTR variants,** a **diagnosis may not always be reached** by confirmed TTR variant alone. **Tissue biopsy** to confirm **TTR amyloid deposition is recommended for accurate diagnosis**

A biopsy can **distinguish confounding comorbidities** in patients with a known TTR variant

To avoid unnecessary repeat procedures and expedite diagnosis, the **experts were in agreement for tissue biopsy** collection from **any patient** with suspected ATTRv amyloidosis **undergoing invasive procedures** (e.g., CTS release surgery or GI endoscopy)

The **sensitivity** and **accuracy** of tissue biopsies **can vary** according to tissue type and study center

A **negative** **biopsy** from a patient with highly suspected ATTRv amyloidoisis **should not exclude a diagnosis**

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In individuals 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 information to aid confirmation of diagnosis

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Mass spectrometry or immunohistochemical analysis of the biopsy sample can **differentiate** between **TTR** and **light chain amyloid**

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Tissue biopsies can be obtained from the **clinically affected organ or** from more easily **accessible tissues**
(skin, abdominal fat pad, salivary glands)

Skin biopsies are easily accessible and practical[22]

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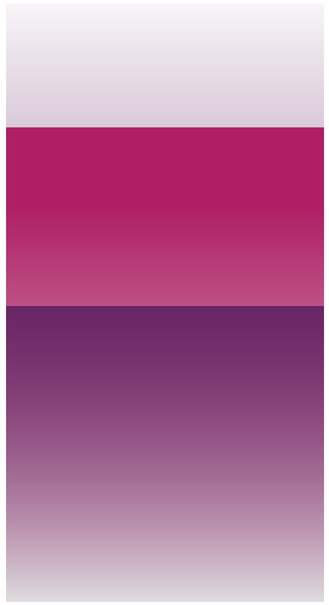
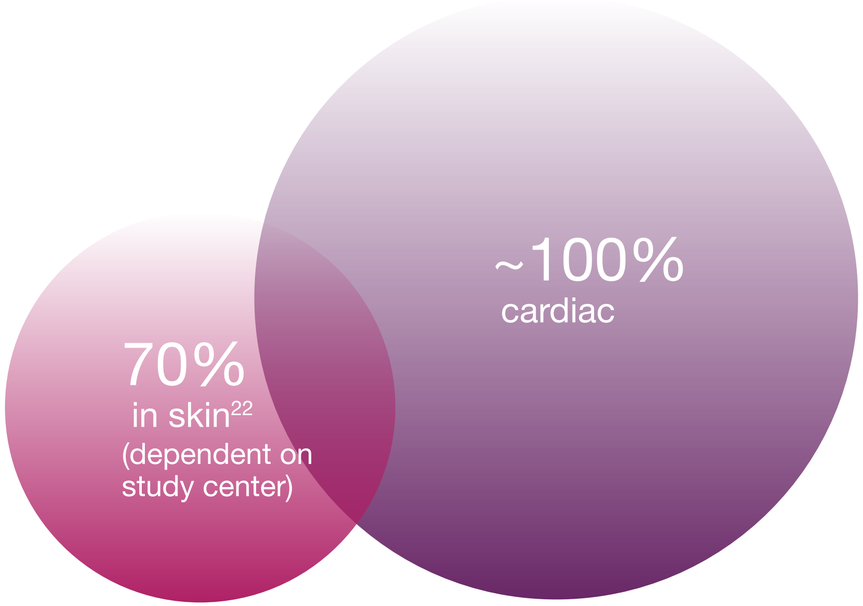
Sensitivity of tissue biopsies



50–80%
is reported in fat pad aspirate[23]



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Other techniques, such as **scintigraphy**, can be used to make a diagnosis in the absence of a positive biopsy

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Asymptomatic Carrier to Symptomatic Patient

Not all TTR variant carriers will develop the disease and **some individuals will remain asymptomatic**

Monitoring pre-symptomatic patients from an **established baseline** ahead of their **predicted age of onset** may allow for early diagnosis

Monitoring should begin approximately

5 years — 10 years

ahead of the predicted age of onset to **determine a "baseline"** for the patient with **follow-up** approximately **every 1–2 years**

Recommended assessments/tools for staging neurologic and cardiac symptoms in patients with symptomatic or pre-symptomatic ATTRv amyloidosis, and frequency for monitoring are shown in **Table 3** and **Table 4**

Contents

Age of onset can be predicted based on a typical age of onset for a specific genotype and age of onset in family members[24,25]; in the US, a family history is less common

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Assessment can begin earlier than recommended if obvious symptoms develop

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Follow-up period will vary depending on genetic variant and expected rate of progression

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Table 3. Recommended assessments/tools for staging or monitoring disease in patients with symptomatic or pre-symptomatic ATTRv amyloidosis

List of assessments for 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 pre-symptomatic variant carriers. Some centers perform only if new symptoms indicative of radiculopathy or CTS, following initial diagnosis. 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. Most centers perform only for clinical trials
Norfolk QOL-DN questionnaire	IIb	1	Annual/every 6 months by those that use in clinical practice. Most centers perform only for clinical trials
COMPASS-31 questionnaire	IIa	2	Annual/every 6 months by those that use in clinical practice. 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

[a]Class I=strong; Class IIa=moderate; Class IIb=weak.
[b]1=very sensitive; 2=sensitive; 3=moderately sensitive.
Adapted from source.

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Table 4. Recommended assessments/tools for staging or monitoring disease in patients with symptomatic or pre-symptomatic ATTRv amyloidosis

List of assessments for non-neurologic symptoms[a]			
Assessment tool	**Strength of recommendation[b]**	**Sensitivity to disease progression (1–3)[c]**	**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

[a]Clinicians should consider a collaborative multispecialty approach to assessment of non-neurologic symptoms to capture the multisystem nature of this disease.[26]
[b]Class I=strong; Class IIa=moderate; Class IIb=weak.
[c]1=very sensitive; 2=sensitive; 3=moderately sensitive.
[d]In patients receiving TTR silencers, prealbumin testing to monitor TTR suppression may provide some reassurance of pharmacologic response to treatment for some patients.
Adapted from source.

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Treatment Initiation Timing and Disease Monitoring

Timing of Treatment Initiation

Long-term extension studies of pharmacotherapies approved in the US for ATTRv (or hATTR) amyloidosis with polyneuropathy indicated that **early intervention** with disease-modifying therapies results in **better patient outcomes**[27,28]

Clinicians should **initiate treatment** in patients **as soon as possible** following a diagnosis

In the future, **biomarkers** such as neurofilament light chain, may allow **early detection** of nerve damage[29–31]

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In the **patisiran Global OLE** and **inotersen NEURO-TTR LTE** studies, patients who had been previously treated with placebo in the Phase 3 studies demonstrated **improvement or stabilization in measures of polyneuropathy** following initiation of disease-modifying therapy

The level of neurologic function did not reach that observed in patients who had received earlier active treatment

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Early detection of nerve damage will facilitate identification of patients transitioning from carrier to symptomatic disease

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Monitoring of Disease in ATTRv Amyloidosis

ATTRv amyloidosis with polyneuropathy is characterized by progressive disability (measured by FAP stage)[32,33]

Recommended tools and assessments for monitoring disease progression are shown in **Table 3** **and Table 4**

A **neurologic assessment** along with a **detailed neurologic examination** is recommended[34] every 6–12 months

Other assessments recommended at baseline and repeated where clinically indicated (e.g new neurologic symptoms) **include electrodiagnostic testing**[34] and patient-reported tools which can monitor impact on symptoms and daily life (i.e., Norfolk QOL-DN, R-ODS, and COMPASS-31)[35–37]

Standard tests for orthostatic hypotension should be routinely undertaken to monitor **autonomic dysfunction**

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Neurologic assessment includes **symptoms of gait, weakness, risk of falls, lightheadedness, GI issues, weight loss,** and **how the patient is feeling**

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If electrodiagnostic tests are repeated, care **must be taken** to replicate exact conditions

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Heart rate variability is a sensitive, although non-specific, marker of cardiac autonomic dysfunction

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Specific autonomic tests should be performed at specialized centers to confirm autonomic dysfunction

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Table 3. Recommended assessments/tools for staging or monitoring disease in patients with symptomatic or pre-symptomatic ATTRv amyloidosis

List of assessments for 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 pre-symptomatic variant carriers. Some centers perform only if new symptoms indicative of radiculopathy or CTS, following initial diagnosis. Some centers will perform annually
Orthostatic BP/vitals	IIa	2	New patient/annually to assess treatment response
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Adapted from source.

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Table 4. Recommended assessments/tools for staging or monitoring disease in patients with symptomatic or pre-symptomatic ATTRv amyloidosis

List of assessments for non-neurologic symptoms[a]			
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- 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
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[d]In patients receiving TTR silencers, prealbumin testing to monitor TTR suppression may provide some reassurance of pharmacologic response to treatment for some patients.
Adapted from source.

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Treatment Choice for ATTRv Amyloidosis with Polyneuropathy in the US

Symptomatic treatments (Table 5) can reduce symptom burden but do not affect the underlying disease pathophysiology

Symptomatic relief ranges from providing physical therapy, supporting devices, and/or different drugs for ease of specific symptoms

There has been an increase in available **disease-modifying treatment strategies** including TTR gene silencers and TTR stabilizers, which improve multisystem manifestations[27,28,38–46]

Treatment Recommendations and Considerations

Use of a TTR **gene silencer**[a] therapeutic is recommended as first-line treatment for **US patients** with **ATTRv amyloidosis with polyneuropathy**

Choice of disease-modifying therapy should take **efficacy, safety, comorbidities,** and **preference for ease of use** into consideration

Choice of treatment should be a **shared decision** between the individual patient and the treating clinician

[a]*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.*

Table 5. Symptom management options for patients with ATTRv amyloidosis with polyneuropathy in the US

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, and 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, stomach ache, diarrhea
	Docusate	Nausea, stomach ache, 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

Adapted from source.

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Table 5. Symptom management options for patients with ATTRv amyloidosis with polyneuropathy in the US

Symptoms/manifestation targeted	Treatment/care management options	Side effects and other considerations for prescribing
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	
	Night-time mask and eye ointment or night-time 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	

Adapted from source.

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Liver transplantation is seldom recommended due to complications and varying efficacy across genotypes[47]

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In patients with prior liver transplantation, **gene silencers may benefit patients** with continued disease progression[48,49]

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Tafamidis is approved in **Europe and Latin America** for the treatment of ATTRv amyloidosis with polyneuropathy, and is **only approved in the US for the treatment of patients with TTR amyloid cardiomyopathy**[50,51]

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The non-steroidal 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. Monitoring for **disease progression** or **side effects** should occur

Once disease progression is observed, switching to a gene silencer therapy is recommended

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Notable Implications Regarding Treatment Choice

Gene silencers are **not currently approved** for treatment of patients with **ATTRv amyloidosis** and **pure cardiac phenotype** R

There is **limited evidence** for the role of combination therapy in patients with ATTRv amyloidosis

None of the currently approved or available therapies have been investigated in patients with **CNS** or **ocular manifestations**

The **efficacy** of disease-modifying treatments in patients with **more advanced disease** (FAP stage 3/PND IV) is **not well characterized,** although treatment with disease-modifying therapy is **still recommended**

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Positive results from the APOLLO-B study demonstrated that **patisiran can provide benefit on functional capacity, quality of life, and exploratory echocardiographic parameters** in patients with ATTR amyloidosis with cardiomyopathy[52]

Exploratory endpoint analysis demonstrated that inotersen and vutrisiran treatment can stabilize or improve several cardiac manifestations in patients with ATTRv amyloidosis with polyneuropathy[53,54]

Alnylam Pharmaceuticals submitted a supplemental New Drug Application (sNDA) to the FDA for patisiran for the treatment of the cardiomyopathy of ATTR amyloidosis based on data from the APOLLO-B study. The FDA subsequently completed their review of the application in 2023 and issued a complete response letter (CRL).

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A small **US proof-of-concept study** was undertaken in 10 patients treated with tolcapone (NCT03591757), a drug that is believed to cross the blood–brain barrier and penetrate the CNS, where stabilization of TTR levels was shown following 4 weeks of treatment

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Longer-Term Disease Management and Response to Treatment

Following the initiation of treatment, patients should be **monitored (Table 3 and Table 4)** at a minimum of every 6 months for **worsening** of or appearance of **new neurologic or cardiac symptoms**

Patients who initially receive the TTR stabilizer, **diflunisal**, for off-label treatment of polyneuropathy, but later exhibit **disease progression** may benefit from **switching** to a TTR gene silencer

There is no clear alternative treatment option if patients exhibit disease progression on TTR gene silencers

Table 3. Recommended assessments/tools for staging or monitoring disease in patients with symptomatic or pre-symptomatic ATTRv amyloidosis

List of assessments for neurologic symptoms			
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Adapted from source.

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The **progressive, degenerative nature of the disease** means that patients are **not expected** to continuously improve

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Symptoms from **different manifestations may not improve** at the same rate

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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**

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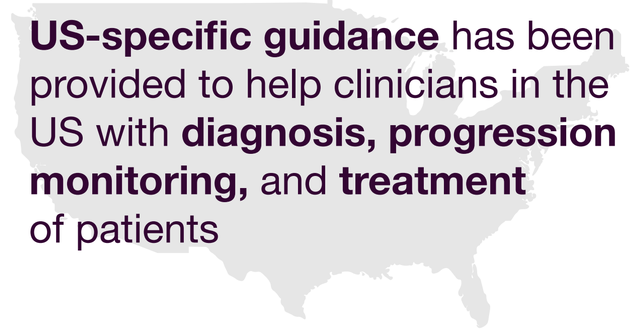
Concluding Remarks

Early disease identification and **timely therapeutic intervention** are key to achieving **better outcomes** for patients with ATTRv amyloidosis with polyneuropathy



US-specific guidance has been provided to help clinicians in the US with **diagnosis, progression monitoring,** and **treatment** of patients

Ongoing clinical trials will continue to provide evidence on key gaps in knowledge

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Summary

Symptoms and Clinical Presentation of ATTRv Amyloidosis with Polyneuropathy

It is difficult to define a typical presentation of ATTRv amyloidosis. Rapidly progressing peripheral sensorimotor neuropathy with accompanying cardiac, autonomic, and/or musculoskeletal manifestations are typical red flags.

Making a Diagnosis of ATTRv Amyloidosis with Polyneuropathy

Early diagnosis and treatment of ATTRv amyloidosis are critical. In patients with suspected ATTRv amyloidosis, genetic testing is essential to confirm a diagnosis. Clinicians should confirm TTR deposition with tissue biopsy in equivocal cases. Monitoring of pre-symptomatic carriers should occur 5–10 years prior to predicted onset with follow-up approximately every 1–2 years.

Treatment Initiation Timing and Disease Monitoring

To improve patient outcomes, treatment should be initiated as early as possible following diagnosis, and disease progression should be monitored using the recommended assessments. Assessments can include neurologic examination, autonomic tests, and patient-reported measures.

Treatment Choice for ATTRv Amyloidosis with Polyneuropathy in the US

Use of a TTR gene silencer therapeutic is recommended as first-line treatment for US patients with ATTRv amyloidosis with polyneuropathy. Choice of disease-modifying therapy should take efficacy, safety, comorbidities, and preference for ease of use into consideration. However, gene silencers are not currently approved for treatment of the cardiomyopathy of ATTRv amyloidosis, CNS, or ocular manifestations.

Longer-Term Disease Management and Response to Treatment

Following the initiation of treatment, patients should be monitored at a minimum of every 6 months for worsening of or appearance of new symptoms. In particular, patients who initially receive the TTR stabilizer, diflunisal, for the off-label treatment of polyneuropathy exhibiting disease progression may benefit from switching to a TTR gene silencer.

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Appendix

Introduction

- Variability in presenting symptoms, gene penetrance, and natural course of the disease results in ATTRv amyloidosis not being considered by clinicians, and many patients experience diagnostic and treatment delays[15,55–57]
- In the US, there is a lack of specific guidance for recognizing symptoms of ATTRv amyloidosis with polyneuropathy
  - Diagnostic algorithms and treatment recommendations for cardiac amyloidosis have been published[58,59]
- Due to the variety of genetic variants, patients in the US exhibit a more heterogeneous disease presentation compared with endemic regions[60,61]
- There remains a need to provide US-relevant guidelines around the polyneuropathy of this disease and its management
- This expert opinion article provides US-specific insights into disease awareness, diagnosis, monitoring, and guidance on the most appropriate treatments for ATTRv amyloidosis with polyneuropathy

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Appendix

Purpose and Methodology

- A panel of seven neurologists with expertise in ATTRv amyloidosis in the US reviewed and discussed the pooled responses from a pre-meeting questionnaire
- This questionnaire was developed by Adelphi Communications Ltd, independently of the sponsor Alnylam Pharmaceuticals, following a literature review of expert recommendation articles, natural history studies, clinical trials outcome data, and non-US management guidelines in ATTRv amyloidosis with polyneuropathy
- These 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
- Manuscript and Interactive Summary funded by Alnylam® Pharmaceuticals (Cambridge, Massachusetts)

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Abbreviations

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; LTE, long-term extension; MRI, magnetic resonance imaging; 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; REMS, Risk Evaluation and Mitigation Strategy; RISC, RNA-induced silencing complex; RNAi, ribonucleic acid interference; R-ODS, Rasch-built Overall Disability Scale; TTE, transthoracic echocardiogram; TTR, transthyretin; US, United States; VP, ventriculoperitoneal; wt, wild-type.

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