# Suspecting and Diagnosing Transthyretin Amyloidosis (ATTR)

For US healthcare professionals only.
Developed by Alnylam Pharmaceuticals, Inc. This resource is for educational purposes only.
The information provided is not intended to serve as recommendations for clinical practice.

## Recognizing Cardiac Manifestations of ATTR[1,2]

**CLINICAL**
- Shortness of breath
- Edema
- Palpitations and arrhythmias
- Fatigue
- Heart failure symptoms
- Family history of heart failure
- Orthostatic hypotension

**IMAGING**
- Increased left ventricular wall thickness
- Grade 2 or worse diastolic function
- Abnormal longitudinal strain with apical sparing
- Diffuse subendocardial or transmural LGE on CMR imaging with increased extracellular volume fraction

**ELECTRICAL**
- Conduction system disease/pacemaker
- Atrial fibrillation
- Pseudoinfarct pattern
- Discordant QRS voltage for degree of increased left ventricular wall thickness on imaging

**LABORATORY**
- Persistent low-level troponin elevation
- Elevated BNP or NT-proBNP

## Diagnosing Suspected ATTR-CM[3-5]

**STEP 1**
Rule out AL amyloidosis with monoclonal light-chain assays

**STEP 2**
Detect amyloid deposition in myocardial tissues with nuclear scintigraphy or cardiac biopsy

**STEP 3**
Once ATTR-CM is confirmed, use genetic testing to determine if it is hereditary

**CLUES FROM HISTORY, ECG, AND IMAGING**

**MONOCLONAL PROTEIN?**
- Abnormal serum kappa/lambda free light chain (depends on eGFR)
- Monoclonal protein on serum/urine IFE

**YES**

**Consultation** with hematologist
**Biopsy** (affected organ/surrogate site)
- Positive Congo red
- Tissue typing by mass spectrometry

**AL-CM**
**Or ATTR-CM with MGUS**

**NO**

**RADIONUCLIDE SCINTIGRAPHY (WITH SPECT)**

**Grade 0 uptake**

**Not consistent with amyloid**

**ATTR-CM unlikely**
Some variants of hATTR are associated with grade 0 $^{99m}$Tc-PYP uptake[5]

**Grade 1 uptake**

- Consider alternative imaging modalities if clinical suspicion is high (non diagnostic)[a]
- Endomyocardial biopsy

**Amyloid**

**Grade 2/3 uptake**

**ATTR-CM**

**GENETIC TESTING**

**hATTR-CM** | **wtATTR-CM**

- Cardiac scintigraphy could be ordered simultaneously for efficiency, but must be interpreted in the context of a negative monoclonal light chain screen
- Avoid false positives: SPECT/CT imaging to exclude blood pool uptake
- Avoid false negatives: consider biopsy if scan is negative/equivocal but clinical suspicion is high

This algorithm has been independently developed by Alnylam based on the references cited and is not endorsed by, affiliated with, or sponsored by the American College of Cardiology or the American Heart Association.

[a]This step is relevant if not already conducted earlier in the patient diagnostic journey to assess clinical suspicion.


**References:**
**1.** Kittleson MM, et al. *J Am Coll Cardiol*. 2023;81:1076-1126; **2.** Adams D, et al. *Orphanet J Rare Dis*. 2021;16:411; **3.** Kittleson MM, et al. *J Am Coll Cardiol*. 2026;87:549-565; **4.** Kittleson MM, et al. *Circulation*. 2020;142:e7-e22; **5.** Dorbala S, et al. *Circ Cardiovasc Imaging*. 2021;14:e000029.


**Abbreviations:**
$^{99m}$**Tc-PYP**, technetium-99m-pyrophosphate; **AL**, amyloid light chain; **AL-CM**, amyloid light chain cardiac amyloidosis; **ATTR**, transthyretin amyloidosis; **ATTR-CM**, transthyretin amyloidosis with cardiomyopathy; **BNP,** brain natriuretic peptide; **CMR**, cardiac magnetic resonance; **CT**, computed tomography; **ECG**, electrocardiogram; **eGFR**, estimated glomerular filtration rate; **hATTR,** hereditary transthyretin amyloidosis; **hATTR-CM**, hereditary transthyretin amyloidosis with cardiomyopathy; **IFE**, immunofixation electrophoresis; **LGE**, late gadolinium enhancement; **MGUS**, monoclonal gammopathy of undetermined significance; **NT-proBNP**, *N*-terminal prohormone of brain-type natriuretic peptide; **SPECT**, single-photon emission computed tomography; **wtATTR-CM**, wild-type transthyretin amyloidosis with cardiomyopathy.



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## Recognizing Extracardiac Manifestations of ATTR[1-3]

### MUSCULOSKELETAL

- Bilateral CTS
- Biceps tendon rupture
- Lumbar spinal stenosis
- Shoulder, knee, and hip pain or surgery
- Trigger finger

### SENSORIMOTOR NEUROPATHY

**Sensory symptoms (early manifestation)**
- Numbness and tingling
- Altered sensation (change in sensitivity to pain or temperature)

**Motor symptoms (late manifestation)**
- Muscle weakness
- Tripping, foot drop
- Difficulty walking or climbing stairs
- Impaired balance/falls

### AUTONOMIC DYSFUNCTION

- Orthostatic hypotension
- Diarrhea or constipation
- Urinary retention (recurrent UTI)
- Erectile dysfunction

### GASTROINTESTINAL MANIFESTATIONS[a]

**Mucosal**
- Malabsorption: bloating, nausea, vomiting, diarrhea

**Neuropathic**
- GI dysmotility: bloating, nausea, vomiting, diarrhea, constipation, gastroparesis, and early satiety

**Vascular**
- GI bleeding, ischemia

## Diagnosing Suspected hATTR-PN[4]

Suspicion of hATTR-PN should be raised in patients who present with sensory or sensorimotor peripheral neuropathy plus any of the risk factors shown below. *TTR* genetic testing and a biopsy to test for amyloid deposition can help confirm an hATTR-PN diagnosis[4]

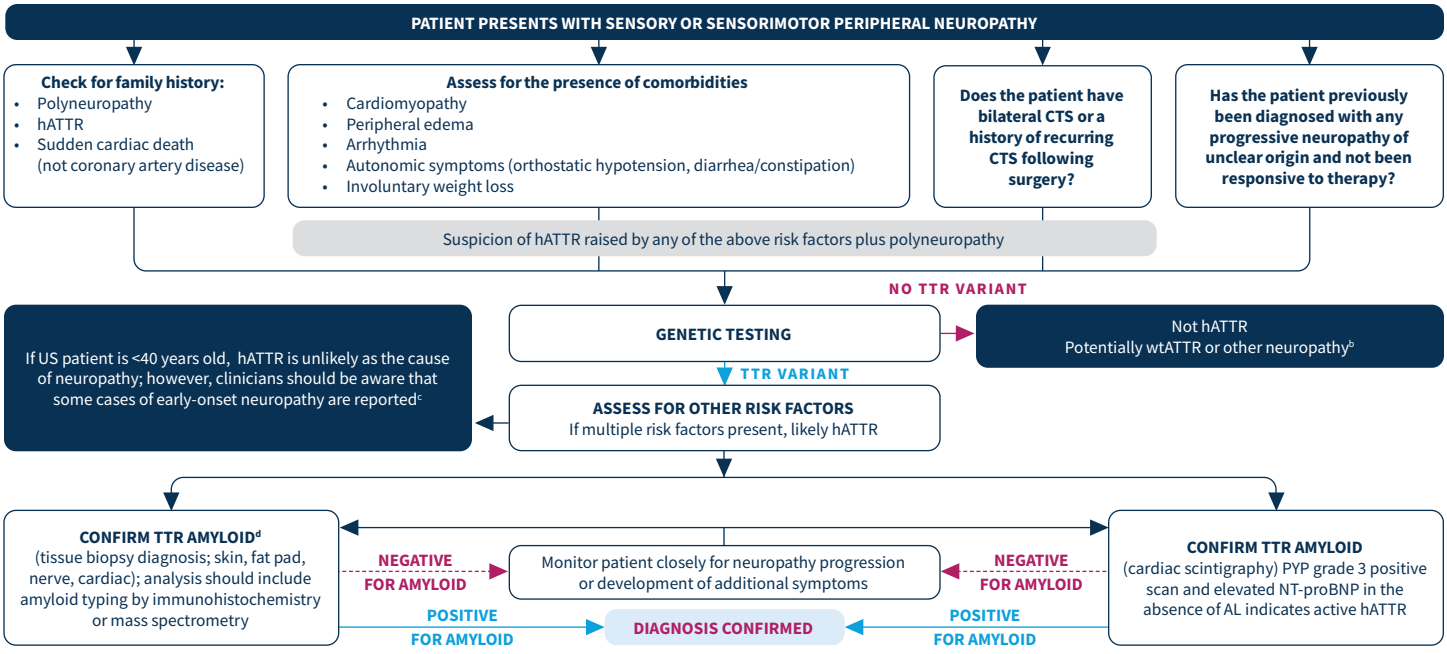


Figure adapted from Karam C, et al. ©2024 The Authors. Licensed under CC-BY-NC. DOI: 10.1002/mus.28026.

[a]GI symptoms may be difficult to attribute to GI amyloid deposition as cardiac involvement and medication side effects may also cause abdominal pain, nausea, diarrhea, or constipation.

[b]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).[4]

[c]Early onset of polyneuropathy has been reported in hATTR.[4]

[d]Importance of tissue diagnosis is greater when concurrent possible causes of peripheral neuropathy (i.e., B12 deficiency, diabetes mellitus, paraproteinemia) 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 hATTR does not exclude a diagnosis, and further investigation (i.e., scintigraphy) or close follow-up is warranted.[4]


**References:**
**1.** Kittleson MM, et al. *J Am Coll Cardiol*. 2023;81:1076-1126; **2.** Bentellis I, et al. *Clin Auton Res*. 2019;(suppl 1):S65-S74; **3.** Adams D, et al. *Orphanet J Rare Dis*. 2021;16:411; **4.** Karam C, et al. *Muscle Nerve*. 2024;69:273-287.


**Abbreviations:**
**AL**, amyloid light chain; **ATTR**, transthyretin amyloidosis; **CTS**, carpal tunnel syndrome; **GI**, gastrointestinal; **hATTR**, hereditary transthyretin amyloidosis; **hATTR-PN**, hereditary transthyretin amyloidosis with polyneuropathy; **NT-proBNP**, *N*-terminal prohormone of brain-type natriuretic peptide; **PYP**, pyrophosphate; **TTR**, transthyretin; **UTI**, urinary tract infection; **wtATTR**, wild-type transthyretin amyloidosis.



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