Transthyretin-mediated amyloidosis (ATTR) is a form of systemic amyloidosis caused by amyloid deposits in tissues and organs derived from TTR (transthyretin) protein, primarily produced in the liver.1

ATTR amyloidosis can be acquired or inherited. Wild-type ATTR (wATTR) amyloidosis presents primarily with cardiac manifestations, whereas hereditary or variant ATTR (hATTR or ATTRv) amyloidosis variably involves the heart and autonomic and peripheral nerves. Inheritance for hATTR amyloidosis is autosomal dominant with variable penetrance.2

Perceived rarity of the disease and clinical manifestations similar to other more common diseases like heart failure can lead to delays in the identification and diagnosis of ATTR amyloidosis. The list of clinical clues and diagnostic testing provided in this quick reference guide are intended to promote earlier identification and accurate diagnosis of ATTR amyloidosis, with subsequent genetic testing to determine if there is a genetic cause. Confirmation of a TTR variant should trigger genetic counseling and potential screening for family members.3

### Clinical Clues3,4,5

<table>
<thead>
<tr>
<th>Traditional Cardiac Clues</th>
<th>Noncardiac Clues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intolerance to antihypertensive or heart failure medications because of symptomatic hypotension or orthostasis</td>
<td>Neurological: sensorimotor polyneuropathy (paresthesias and weakness), autonomic dysfunction (orthostatic hypotension, postprandial diarrhea alternating with constipation, gastroparesis, urinary retention, and incontinence)</td>
</tr>
<tr>
<td>Persistent low-level elevation in serum troponin</td>
<td>Orthopedic: carpal tunnel syndrome, lumbar spinal stenosis, unprovoked biceps tendon rupture, hip and knee arthroplasty</td>
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<tr>
<td>Discordance between QRS voltage on an ECG and wall thickness on imaging</td>
<td>Black race</td>
</tr>
<tr>
<td>Unexplained atrioventricular block or prior pacemaker implantation</td>
<td>Family history of polyneuropathy</td>
</tr>
<tr>
<td>Unexplained LV wall thickening, right ventricular thickening, or atrial wall thickening</td>
<td></td>
</tr>
<tr>
<td>Family history of cardiomyopathy</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** LV, left ventricular

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### References


**Diagnostic Testing for Suspected hATTR Amyloidosis with Cardiomyopathy**

**Abbreviations:**
- ECG: electrocardiogram
- HCM: hypertrophic cardiomyopathy
- CMR: cardiovascular magnetic resonance imaging
- AL-CM: amyloid light-chain cardiomyopathy
- IFE: immunofixation electrophoresis
- Tc-99m-PYP: technetium-99m-pyrophosphate
- H/CL: heart-to-contralateral lung

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**Hematology Consultation**
- Biopsy of involved organ (cardial/renal)
  - Positive Congo Red
  - Tissue typing by mass spectrometry (preferred) or immunohistochemistry (if appropriate expertise)

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**Cardiac amyloidosis unlikely**
- ATTR-CM
- Genetic testing

**Screen for presence of a monoclonal light chain**
- Serum kappa/lambda free light chain ratio (abnormal if ratio is < 0.26 or > 1.65)
- Serum IFE (abnormal if monoclonal protein detected)
- Urine IFE (abnormal if monoclonal protein detected)

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**Tc-99m-PYP available?**
- Yes
  - Tc-99m-PYP
    - Grade 2/3 uptake OR
    - H/CL ratio > 1.5
    - Cardiac amyloidosis unlikely
  - Yes
    - Genetic testing
    - Yes
      - ATTRv-CM
      - ATTRwt-CM
    - No
      - Cardiac amyloidosis unlikely

---

**Endomyocardial biopsy**
- Positive Congo Red
- Tissue typing by mass spectrometry or immunostaining
- Consider heart biopsy if suspicion high

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**Diagnostic Testing for Suspected hATTR Amyloidosis with Polyneuropathy**

**Clinical suspicion of amyloid neuropathy** → **Confirmation of ATTRv amyloidosis** → **Patient follow-up after diagnosis**

**DNA sequencing**
- Analysis of the amyloidogenic TTR variant

**Amyloid typing**
- Immunohistochemistry or mass spectrometry

**Biopsy of amyloid deposition**
- Possible biopsy sites: Labial salivary gland; subcutaneous fatty tissue of abdominal wall; skin; kidney; nerve; gastrointestinal tract including submucosa
  - Congo red staining with characteristic green birefringence under polarized light

**Clinical examination every 6 months (every 3 months for stages II/III) unless responding well to treatment**

**Neurology**
- New or progressed symptoms
- Functional scores (eg, walking ability, polyneuropathy disability, neurological impairment score)
- Autonomic (eg, bladder/urinary tract infection, orthostatic hypotension, erectile dysfunction, and gastrointestinal disturbances including diarrhea and early satiety)

**Cardiology**
- Electrocardiography
- Echocardiography and NT-proBNP

**Ophthalmology**
- Modified body mass index, weight

**Abbreviations:**
- NT-proBNP: N-terminal pro-brain natriuretic peptide

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