In hATTR amyloidosis....

DISEASE PROGRESSION **UNRAVELS** THEIR LIVES

The progression of hereditary ATTR amyloidosis can pull apart your patients' futures.[1] Identifying the disease early may help patients hold on to their physical function, independence, and well-being.[2-5]

Alnylam® PHARMACEUTICALS

hATTR amyloidosis is a multisystem, rapidly progressive, often fatal disease[2,6,7]

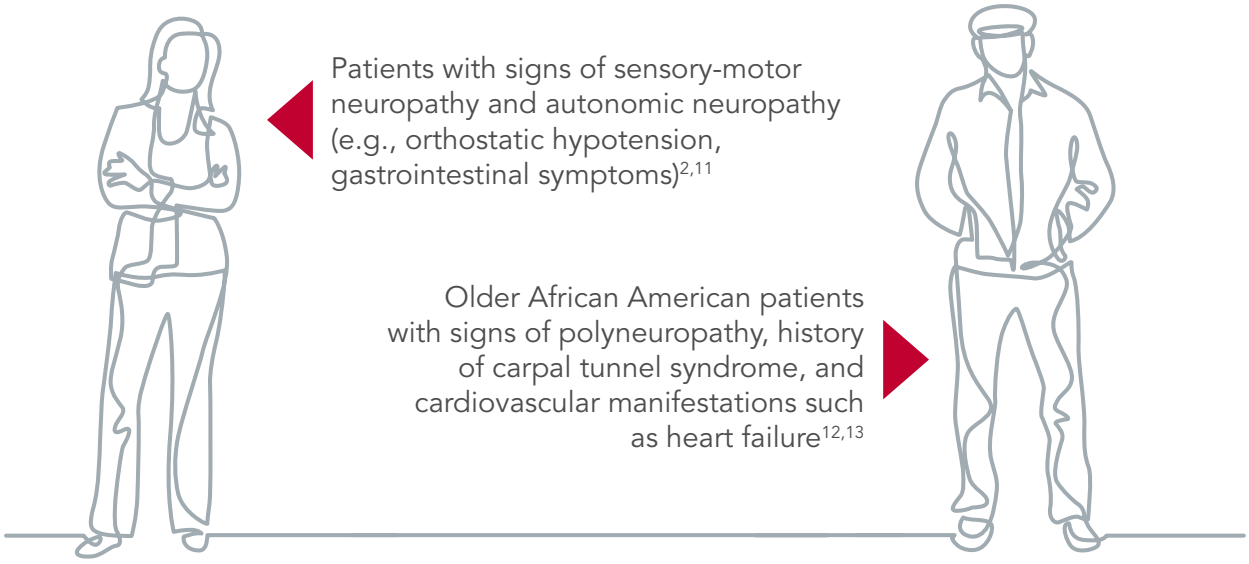
Hereditary transthyretin-mediated (hATTR) amyloidosis is a disease caused by one of many possible variants in the transthyretin (TTR) gene. TTR proteins misfold, then aggregate into amyloid deposits, resulting in highly varied and progressive sensory-motor and autonomic neuropathy and cardiac symptoms.[2,6,7]

An estimated 50,000 patients worldwide are affected by the condition.[8]

hATTR amyloidosis is inherited in an autosomal dominant manner. The other type of ATTR amyloidosis is wild-type ATTR amyloidosis, for which the etiology is unknown, but is presumed to be associated with aging.[6,9]

By the time patients receive a diagnosis of hATTR amyloidosis, the median survival is 4.7 years.[2,10]

hATTR amyloidosis patients may already be in your practice



Examples of patients with hATTR amyloidosis. Age of onset and symptom presentation may vary from patient to patient.[2]

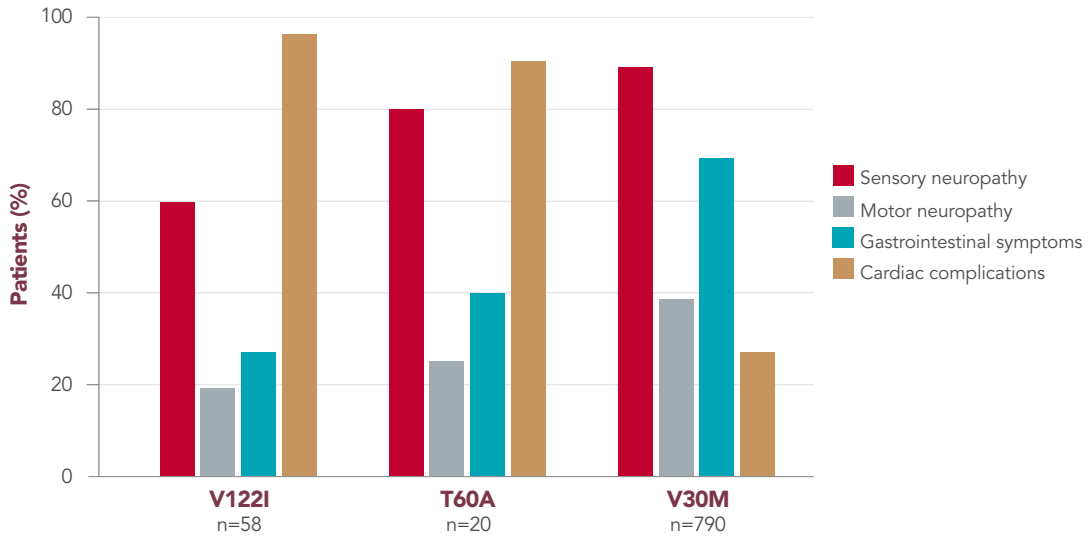
The rapid progression of hATTR amyloidosis can lead to significant dysfunction, declining quality of life, and premature death.[1,2,6,7]

Multisystem dysfunction is a reality for most patients[6]

hATTR amyloidosis often leads to multisystem involvement[6]

- Although there is some association between variant and symptom presentation, most patients suffer from overlapping symptoms of sensory-motor neuropathy, autonomic neuropathy, and cardiac manifestations[6]
- The most common variants in the United States are V122I, T60A, and V30M[12,14]
- Polyneuropathy may precede or coincide with cardiomyopathy, even in patients with the V122I variant[15]

SYMPTOM PRESENTATION BY VARIANT[16,a,b]



What you should know about V122I

- V122I is the most common variant in the United States and is prevalent in ~4% of African Americans[6,12,17,18]
- A majority of individuals with a V122I variant have polyneuropathy symptoms, including sensory, motor, and gastrointestinal symptoms[12,16,19]
- In a global registry of patients with ATTR amyloidosis, 60% with the V122I variant had sensory neuropathy[16]

[a]Not representative of all possible TTR gene variants.

[b]Data collected by the THAOS registry.

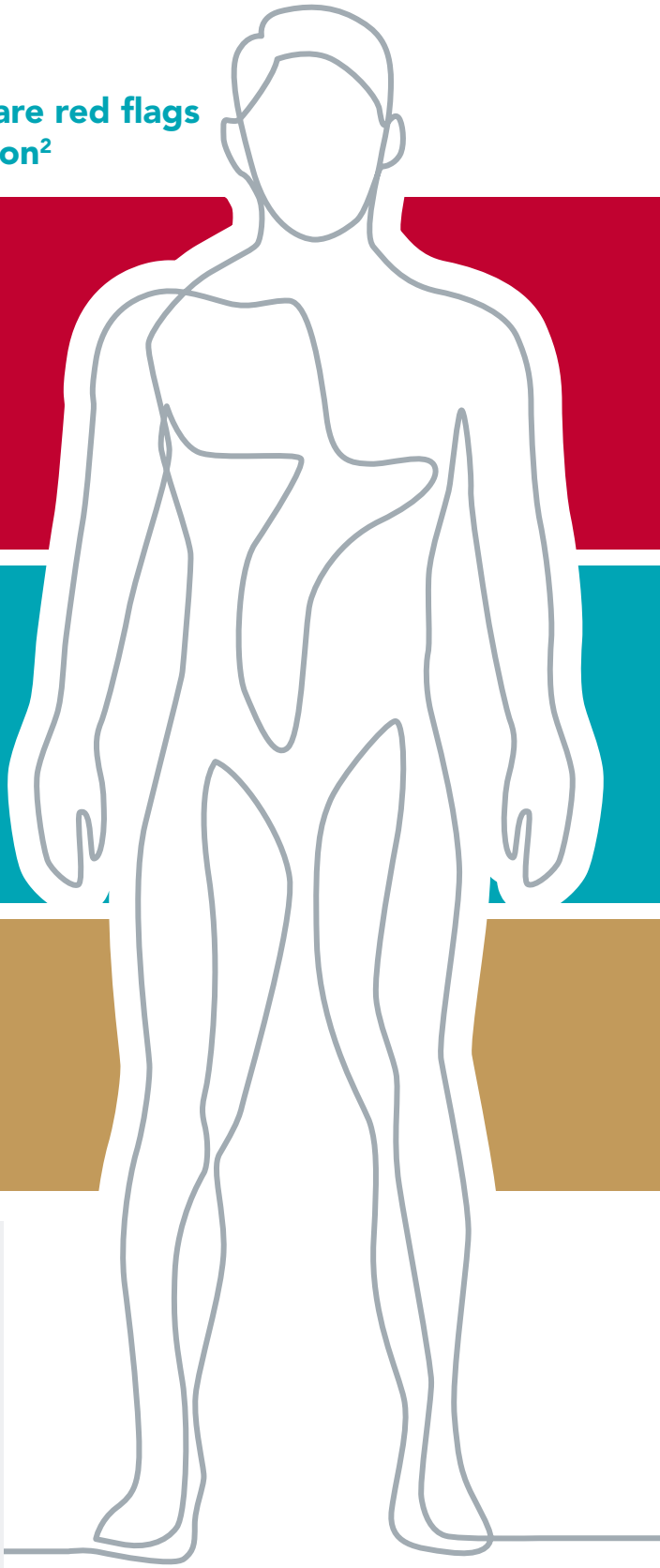
THAOS=Transthyretin-associated Amyloidosis Outcomes Survey.

A multisystem disease takes a toll on the whole body[6]

Family history and multisystem involvement are red flags of hATTR amyloidosis and require urgent action[2]

Sensory-motor neuropathy[2,6]

- Length-dependent neuropathic pain and numbness
- Altered sensation
- Weakness
- Difficulty walking
- Bilateral carpal tunnel syndrome



Autonomic neuropathy[2,6]

- Orthostatic hypotension
- Diarrhea, constipation, nausea and vomiting
- Unintentional weight loss
- Recurrent urinary tract infections
- Sexual dysfunction

Cardiac manifestations[20]

- Conduction abnormalities
- Arrhythmias
- Heart failure
- Left ventricular hypertrophy

Additional signs[2,20]

- Family history of hATTR amyloidosis symptoms or diagnosis
- Rapid symptom progression
- Failure to respond to immunomodulatory treatment
- Intolerance of commonly used cardiovascular medications

Not a comprehensive list of all the symptoms associated with hATTR amyloidosis. Each patient may not experience all of these symptoms, or may not experience them at the same time.

Disease progression leads to daily suffering, rapid decline, and premature death[1]

Progression of sensory-motor neuropathy[6,21-23]

- Sensory loss can reduce dexterity and temperature sensation
- Motor deficits result in progressive weakness and impaired ambulation
- **Sensory-motor neuropathy can progress more than 10x faster than diabetic neuropathy**

Progression of autonomic neuropathy[16,22-28]

- Orthostatic hypotension can cause syncope and sudden falls
- Gastrointestinal issues can cause patients to isolate themselves from social situations
- Continuous weight loss leads to wasting and reduced survival
- Autonomic neuropathy can induce fatal arrhythmias

Progression of cardiac manifestations[20,29-31]

- Significant and measurable decline in cardiac function results in heart failure
- Heart failure due to hATTR amyloidosis progresses more quickly than with other cardiac conditions

Progression of polyneuropathy leads to significant disability.[1]

A timely diagnosis is critical for early intervention[2]

Patients with hATTR amyloidosis may not receive a diagnosis until 3 to 6 years after symptom onset, resulting in significant disease progression. When diagnosis is delayed, entire families may be affected. Genetic testing is a key step in confirming a diagnosis and providing answers for family members at risk.[6,10,32,33]

Consider this 3-step process to ensure an accurate diagnosis.

1. Raise clinical suspicion

- Inquire about a family history of hATTR amyloidosis symptoms
- Look for multisystem dysfunction
- Consider further evaluation of patients with carpal tunnel syndrome, biceps tendon rupture, or spinal stenosis[6,34-36]
- Reevaluate previous diagnoses for similar conditions, especially for patients who continue to worsen or who do not respond to treatment

Some common misdiagnoses include:

- Chronic inflammatory demyelinating polyneuropathy (CIDP)[2,33]
- Amyotrophic lateral sclerosis (ALS)[37]
- Diabetic polyneuropathy[6,33]
- Idiopathic polyneuropathy[33]
- Lumbar spinal stenosis[38]
- Charcot-Marie-Tooth disease (CMT)[33]
- Alcoholic neuropathy[6]
- Hypertensive heart disease[39]
- Hypertrophic cardiomyopathy[39]
- Fabry disease[6]
- Other types of amyloidoses[2,6,22,40-42]

2. Identify the signs through diagnostic tools[6,22,40,a]

Several types of assessments are available to help identify the signs of hATTR amyloidosis.

Sensory-motor assessments	Autonomic assessments	Cardiac assessments
• Electromyography (EMG) • Nerve conduction study (NCS)	• Heart rate deep breathing • Tilt table	• Electrocardiography (ECG) • Echocardiography (Echo) • Cardiac magnetic resonance imaging (CMRI)

[a]Not a comprehensive list of diagnostic tools.

3. Establish a diagnosis[6,38,40,43,a]

To establish the presence of amyloid:

- Nuclear scintigraphic imaging (^{99m}Tc-PYP or ^{99m}Tc-DPD)
- Tissue biopsy + Congo Red (e.g., fat pad, heart, nerve)

To confirm a TTR variant:

- Genetic testing

Alnylam Act® — genetic testing and counseling

Alnylam Act® offers third-party genetic screening and counseling programs at no charge for patients who may have hATTR amyloidosis.

- Alnylam Act® is available for patients 18 years and older who may be at risk for carrying a genetic variant known to be associated with hATTR amyloidosis

Visit **www.invitae.com/alnylam-act-ttr** to learn more about Alnylam Act® and to order a genetic test.

The Alnylam Act® program was created to provide access to genetic testing and counseling to patients as a way to help people make more informed decisions about their health.

- While Alnylam provides financial support for this program, tests and services are performed by independent third parties
- Healthcare professionals must confirm that patients meet certain criteria to use the program
- Alnylam receives de-identified patient data from this program, but at no time does Alnylam receive patient-identifiable information. Alnylam uses healthcare professional contact information for research and commercial purposes
- Genetic testing is available in the US and certain other countries. Genetic counseling is available in the US
- Healthcare professionals or patients who use this program have no obligation to recommend, purchase, order, prescribe, promote, administer, use, or support any Alnylam product
- No patients, healthcare professionals, or payers, including government payers, are billed for this program

[a]Not a comprehensive list of diagnostic tools.

^{99m}Tc-DPD=technetium-^{99m}-3,3-diphosphono-1,2-propanodicarboxylic acid; ^{99m}Tc-PYP=technetium-^{99m}-pyrophosphate.

Rapid disease progression requires an early diagnosis[44]

- Most patients experience multisystem dysfunction and a range of symptoms including sensory-motor neuropathy, autonomic neuropathy, and cardiac manifestations[6]
- Progressive accumulation of amyloid deposits in various systems of the body results in worsening symptoms[7]
- Rapid progression of polyneuropathy severely impacts how patients feel and function, leading to daily suffering, decline in quality of life, and premature death[1]

Alnylam Act® is one option for genetic testing, which can help confirm a diagnosis of hATTR amyloidosis.

Alnylam Act® offers third-party genetic screening and counseling programs at no charge for patients who may have hATTR amyloidosis.

AlnylamAct®

Find out more at www.invitae.com/alnylam-act-ttr.

Start the fight against disease progression by visiting www.hATTRamyloidosis.com.

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