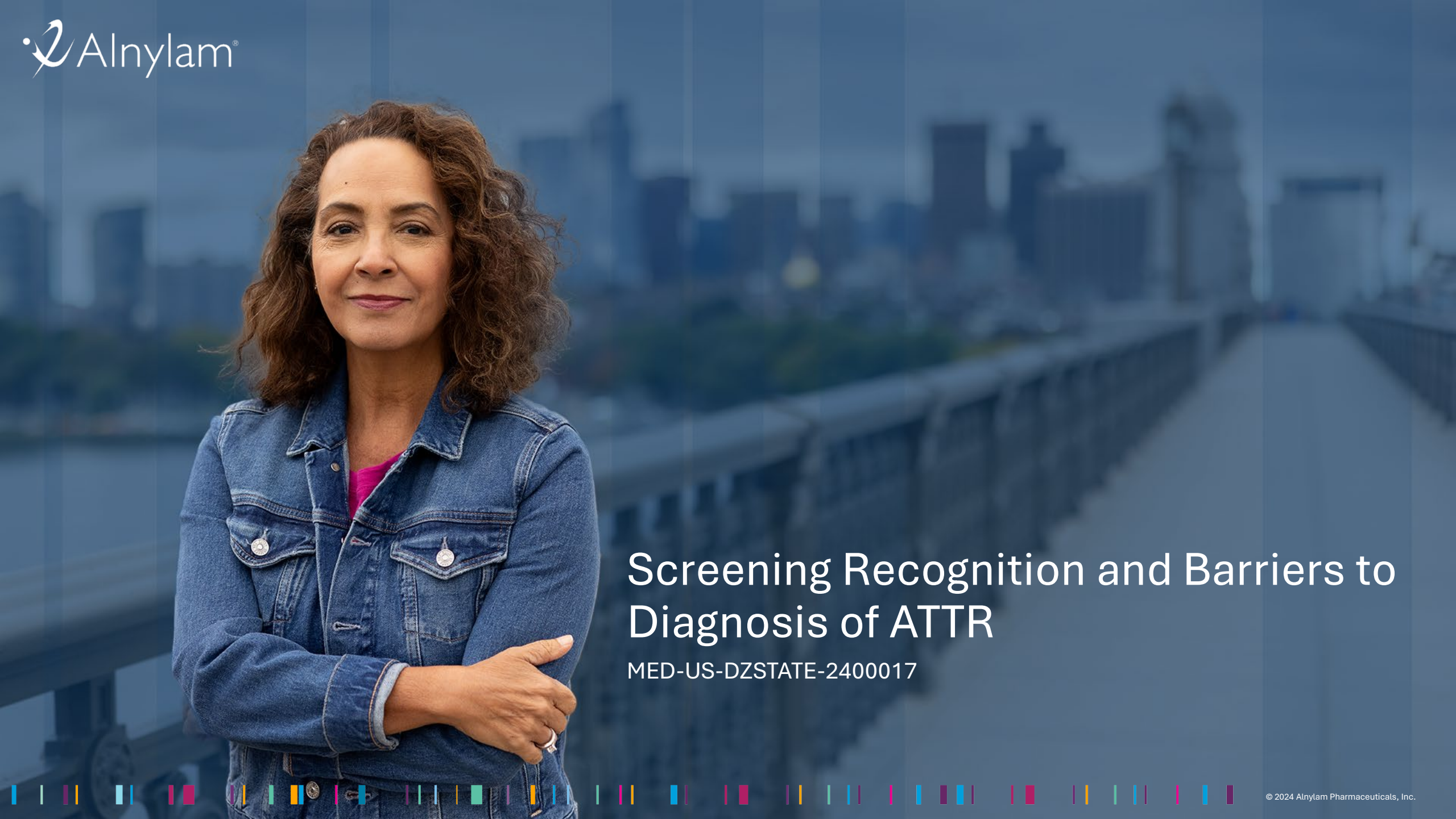


Screening Recognition and Barriers to Diagnosis of ATTR

MED-US-DZSTATE-2400017

ATTR Disease State Slide Deck

- This resource provides information about ATTR.
- This resource is intended to be viewed in its entirety to support scientific exchange and is not intended as recommendations for clinical practice.
- This resource may contain hyperlinks that are not functional in this format.
- For further information, please see RNAiScience.com to connect with a Medical Science Liaison, submit a medical information request, or access other Alnylam medical education resources.

Alnylam®

Screening, Recognition, and Barriers to Diagnosis

Alnylam®

Increasing Clinical Suspicion

Improving recognition of overlapping conditions, misdiagnosis and multiorgan presentation[1]

- Diversity of diagnostic clues can manifest in a patient across many years
- Non-cardiac red flags often precede the diagnosis of ATTR

Patient reported diagnostic journey

Symptom timeline in patients with hATTR

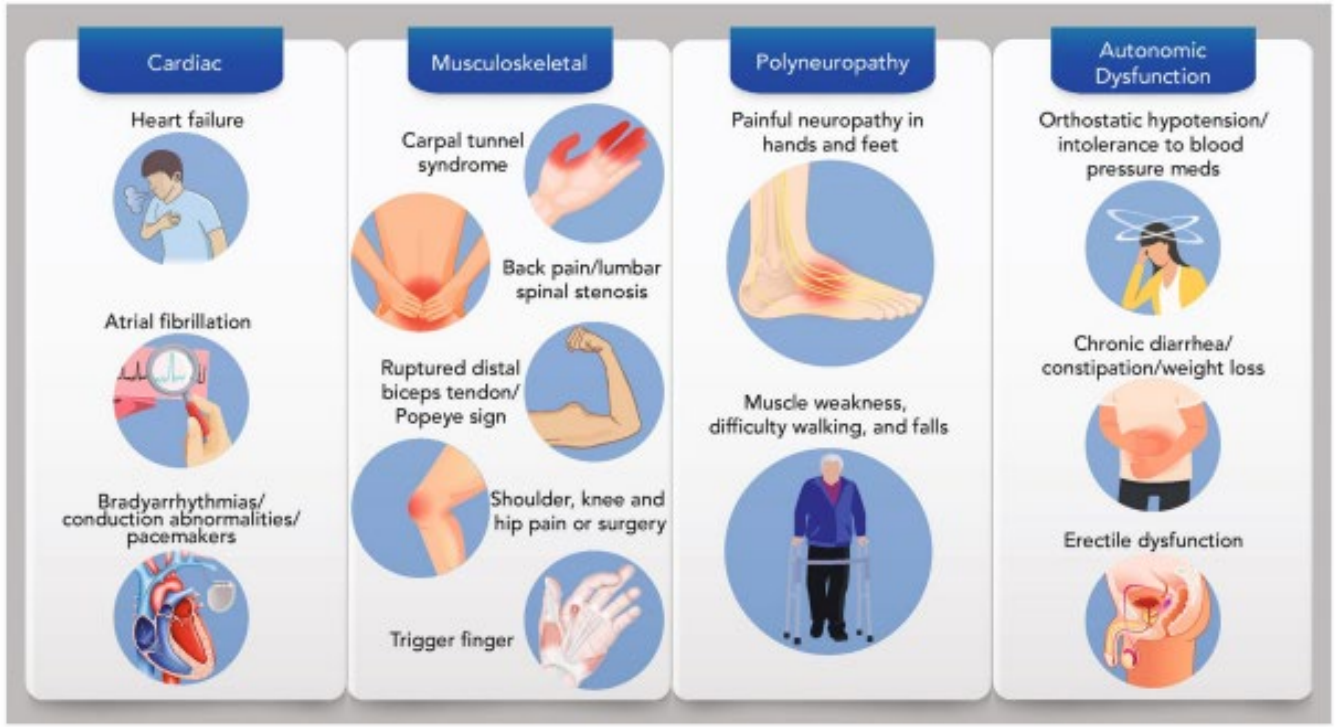


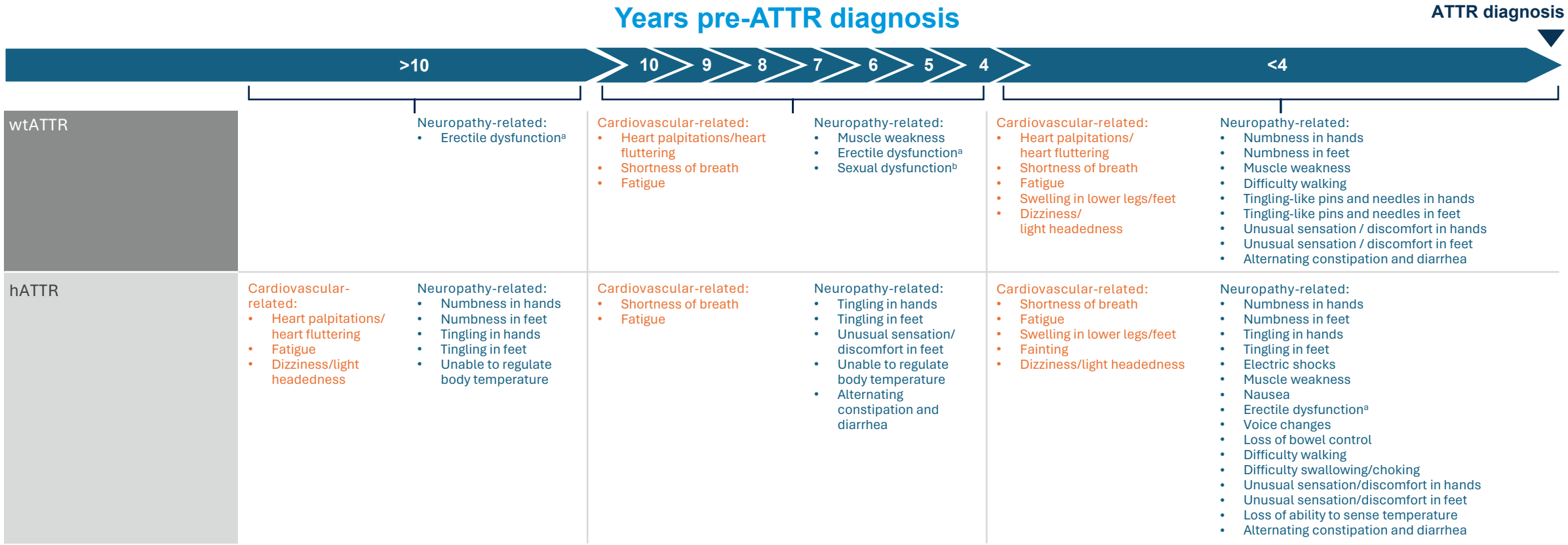
Figure taken from Nativi-Nicolau et al. 2022[1]

hATTR, hereditary ATTTR

1. Nativi-Nicolau et al. Heart Fail Rev. 2022;27(3):785–93.

Patient-reported Diagnostic Journey

Symptoms may start more than 10 years before diagnosis and appear to accumulate over time

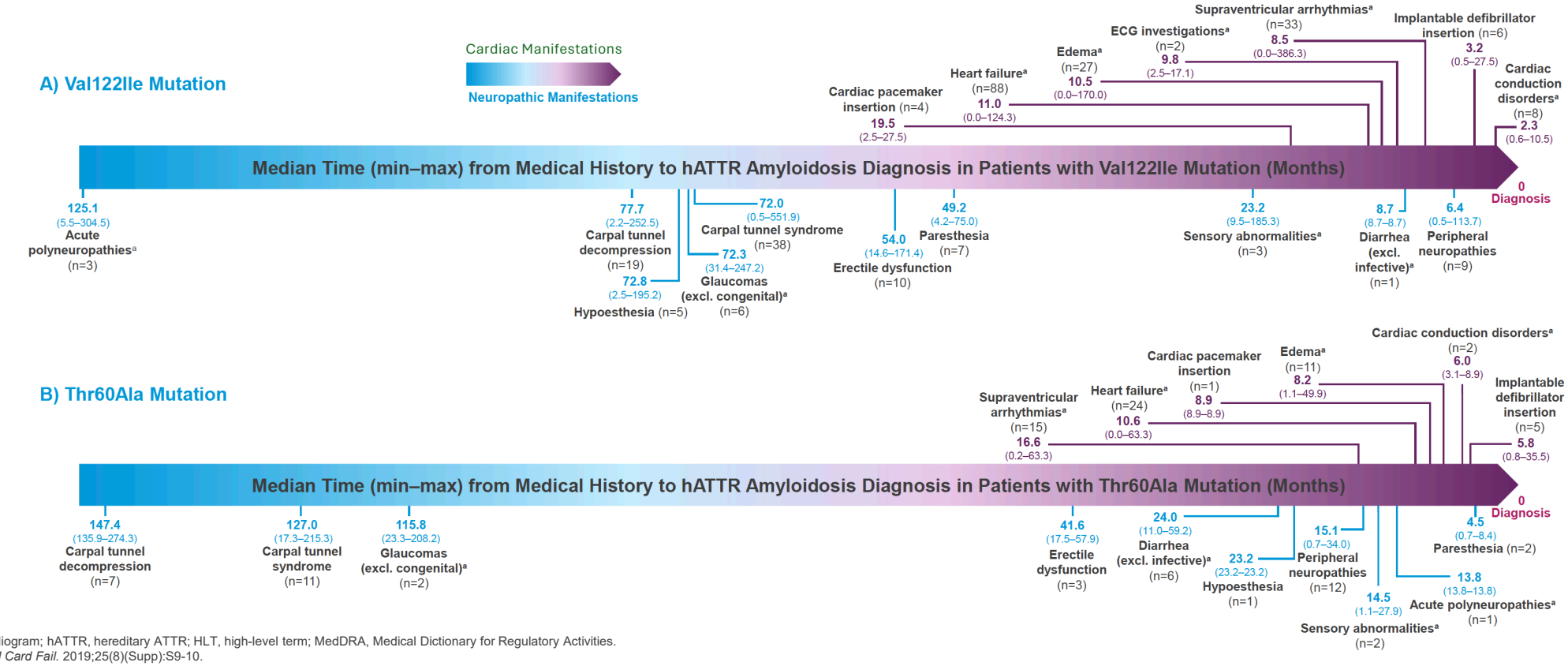


[a]Male only. [b]Female only.
Figure taken from Karam et al. 2022[1]

1. Karam et al. Meeting of the International Society of Amyloidosis. 2022; Poster P192.

Symptom Timeline in Patients with V122I and T60A hATTR

Median time from medical history to hATTR diagnosis for common clinical manifestations



- [a]MedDRA HLT
- ECG, electrocardiogram; hATTR, hereditary ATTR; HLT, high-level term; MedDRA, Medical Dictionary for Regulatory Activities.
- 1. Grogan et al. *J Card Fail.* 2019;25(8)(Supp):S9-10.

Misdiagnosis of ATTR

Overlapping neurologic conditions and misdiagnoses of ATTR[1]

- Idiopathic (small-fiber) neuropathy
- Diabetic neuropathy
- Alcohol neuropathy
- Chronic inflammatory demyelinating polyneuropathy
- Motor neuron disease/ALS
- Fibromyalgia
- Occupational carpal tunnel syndrome
- Malignancy or autoimmune disease

Overlapping cardiac conditions and misdiagnoses of ATTR[2]

- Heart failure with preserved ejection fraction
- Hypertensive cardiomyopathy
- Aortic stenosis
- Hypertrophic cardiomyopathy
- Light chain amyloidosis with cardiac involvement
- Idiopathic restrictive cardiomyopathy
- Iron overload
- Other infiltrative cardiomyopathies (eg, Fabry disease)

ALS, amyotrophic lateral sclerosis; ATTR, transthyretin amyoidosis.

1. Karam et al. *Muscle Nerve*. 2024. Published online January 4, 2024. doi: 10.1002/mus.28026.; 2. Nativi-Nicolau et al. *Heart Fail Rev*. 2022;27:785–93.

Awareness of High-Risk Populations Serves as a Key to an Early Diagnosis of ATTR-CM

High-risk population	Prevalence of ATTR-CM
Atrial fibrillation 	• Studies have reported variable AF prevalence rates of 15-70% in patients with ATTR-CM[1]
HFpEF 	• Cardiac amyloidosis, predominantly ATTR, is suspected to account for 6-30% of HFpEF cases[2] • A cross-sectional analysis found ~13% of patients admitted for HFpEF, ≥60 years old and LV wall thickness ≥12 mm, were found to have wtATTR[3,4]
Left ventricular hypertrophy 	• A cross-sectional study revealed that 5.7% of patients with unexplained LVH and an initial diagnosis of hypertrophic cardiomyopathy had hATTR[5]
Aortic stenosis 	• Approximately 16% of patients admitted with severe calcific AS undergoing percutaneous TAVR screened positive for ATTR-CM[6]
Extracardiac musculoskeletal manifestations 	• Carpal tunnel syndrome, spinal stenosis, or spontaneous biceps tendon rupture may present as "red flags" for ATTR-CM[2] — CTS, primarily affecting those ≥50 years is found in 15-60% of patients with ATTR-CM — CTS may manifest prior to cardiac symptoms, serving as an early sign of disease

AF, atrial fibrillation; AS, aortic stenosis; ATTR, transthyretin amyloidosis; ATTR-CM, ATTR with cardiomyopathy; wtATTR, wild-type ATTR; CTS, carpal tunnel syndrome; CV, cardiovascular; HFpEF, heart failure with preserved ejection fraction; LV, left ventricle; LVH, left ventricular hypertrophy; TAVR, transcatheter aortic valve replacement.

1. Griffin et al. *JACC.* 2021;3(4):488–505; 2. Brito et al. *Glob Heart.* 2023;18(1):59; 3. Gonzalez-Lopez et al. *Eur Heart J.* 2015;36:2585–94; 4. Castano et al. *Curr Cardiovasc Risk Rep.* 2017;11:17; 5. Damy et al. *Eur Heart J.* 2016;37(23):1826-1834; 6. Castano et al. *Eur Heart J.* 2017;38(38):2879–87.

Diagnostic Challenges

ATTR is often underdiagnosed or misdiagnosed, leading to a delay in treatment and/or initiation of potentially detrimental treatments[1]

Barriers to diagnosis identified in a global online patient survey conducted by the ARC[2]

hATTR

Average physicians seen prior to correct diagnosis

32%

Reported misdiagnosis

26%

Reported trouble getting tested

19%

Reported trouble finding a specialist

wtATTR

Average physicians seen prior to correct diagnosis

18%

Reported misdiagnosis

7%

Reported trouble getting tested

14%

Reported trouble finding a specialist

- ARC, Amyloidosis Research Consortium; ATTR, transthyretin amyloidosis; hATTR, hereditary ATTR; wtATTR, wild-type ATTR.
- 1. Nativi-Nicolau et al. Heart Fail Rev. 2022;27(3):785–93; 2. Amyloidosis Research Consortium. ARC 2022 Community Survey Results. Published 2022. Accessed November 6, 2023. https://arci.org/arc-2022-community-survey/#wild.

Summary

- ATTR is a multisystemic, rapidly progressive, debilitating, and fatal disease caused by misfolded TTR accumulating as amyloid deposits in multiple organs and tissues including nerves, heart, and GI tract [1-4]
  - Patients diagnosed with hATTR and wtATTR have a median survival of 4.7[5] and 2.5-5.5 years,[6-8] respectively
- ATTR remains underdiagnosed or misdiagnosed[4,9,10]
- Patients with ATTR experience substantial burden, including reduced QoL[11-14] and functional impairment[6,15]

There remains a need for health care professionals to:

1	2	3	4
Recognize the constellation of red-flag symptoms of ATTR [16,17]	**Collaborate with a multidisciplinary team for a potential diagnosis[16,17]**	**Employ the diagnostic algorithm and confirmatory diagnostic tools to verify diagnosis[17-19]**	**Assess progression of disease following treatment and provide patient with holistic care (mental, physical, and social support)[20,21]**

ATTR, transthyretin amyloidosis; hATTR, hereditary ATTR; wtATTR, wild-type ATTR; GI, gastrointestinal; QoL, quality of life; TTR, transthyretin.

1. Hanna. *Curr Heart Fail Rep.* 2014;11:50–7; 2. Mohty et al. *Arch Cardiovasc Dis.* 2013;106:528–40; 3. Adams et al. *Neurology.* 2015;85:675–82; 4. Maurer et al. *Circ Heart Fail.* 2019;12:e006075; 5. Swiecicki et al. *Amyloid.* 2015;22:123–31; 6. Lane et al. *Circulation.* 2019;140:16–26; 7. Aus dem Siepen et al. *Clin Res Cardiol.* 2018;107(2):158–69; 8. Givens et al. *Aging health.* 2013;9(2):229–35; 9. Hawkins et al. *Ann Med.* 2015;47:625–38; 10. Castano et al. *Heart Fail Rev.* 2015;20:163–78; 11. Coehlo et al. *Muscle Nerve.* 2017;55:323–32; 12. Vinik et al. *J Peripher Nerv Syst.* 2014;19:104–14; 13. Ines et al. *ISPOR Congress* 2015. Poster N21; 14. Obici et al. *Amyloid.* 2020;27:153–62; 15. Bolte et al. *Orphanet J Rare Dis* 2020;15:287; 16. Nativi-Nicolau et al. *Heart Fail Rev.* 2022;27(3):785–93; 17. Kittleson et al. *JACC.* 2023; 81(11):1076–176; 18. Namiranian and Geisler. *Am J Med.* 2022;135 Suppl 1:S13–19; 19. Ando et al. *Orphanet J Rare Dis.* 2013;8:31; 20. Adams et al. *Orphanet J Rare Dis.* 2021;16:411; 21. Obici et al. *BMJ Open.* 2023;13:e073130.

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