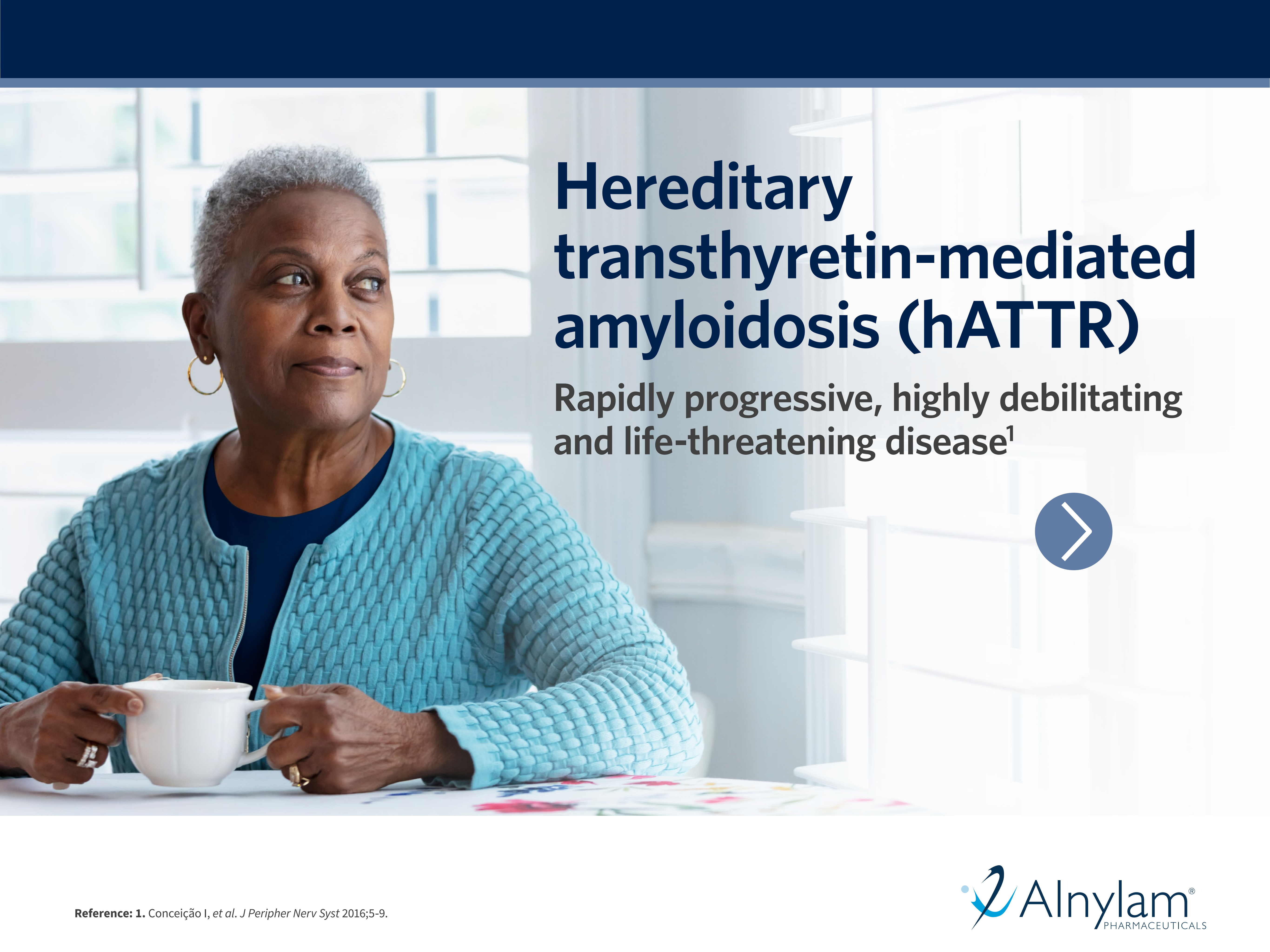
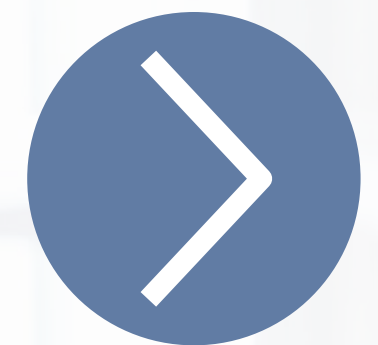




Hereditary transthyretin-mediated amyloidosis (hATTR)

Rapidly progressive, highly debilitating and life-threatening disease¹



Patients with hATTR may already be in your practice

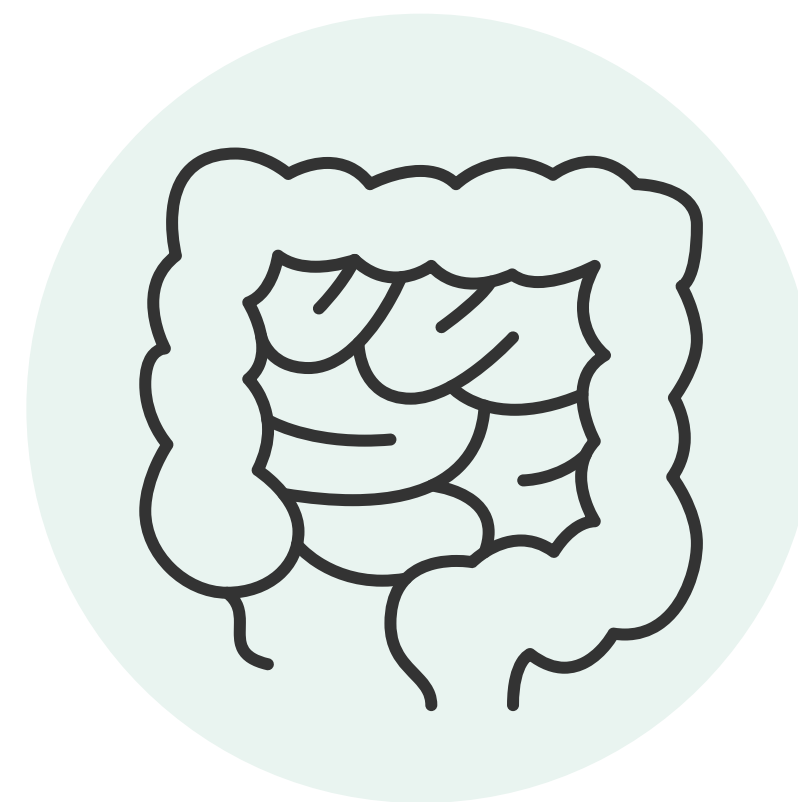
Do you have patients that present with symptoms of progressive symmetric sensory-motor polyneuropathy who also have:^{1,2}



Bilateral carpal tunnel syndrome?



Autonomic symptoms
(i.e., orthostatic hypotension, urinary retention or incontinence, or erectile dysfunction)?



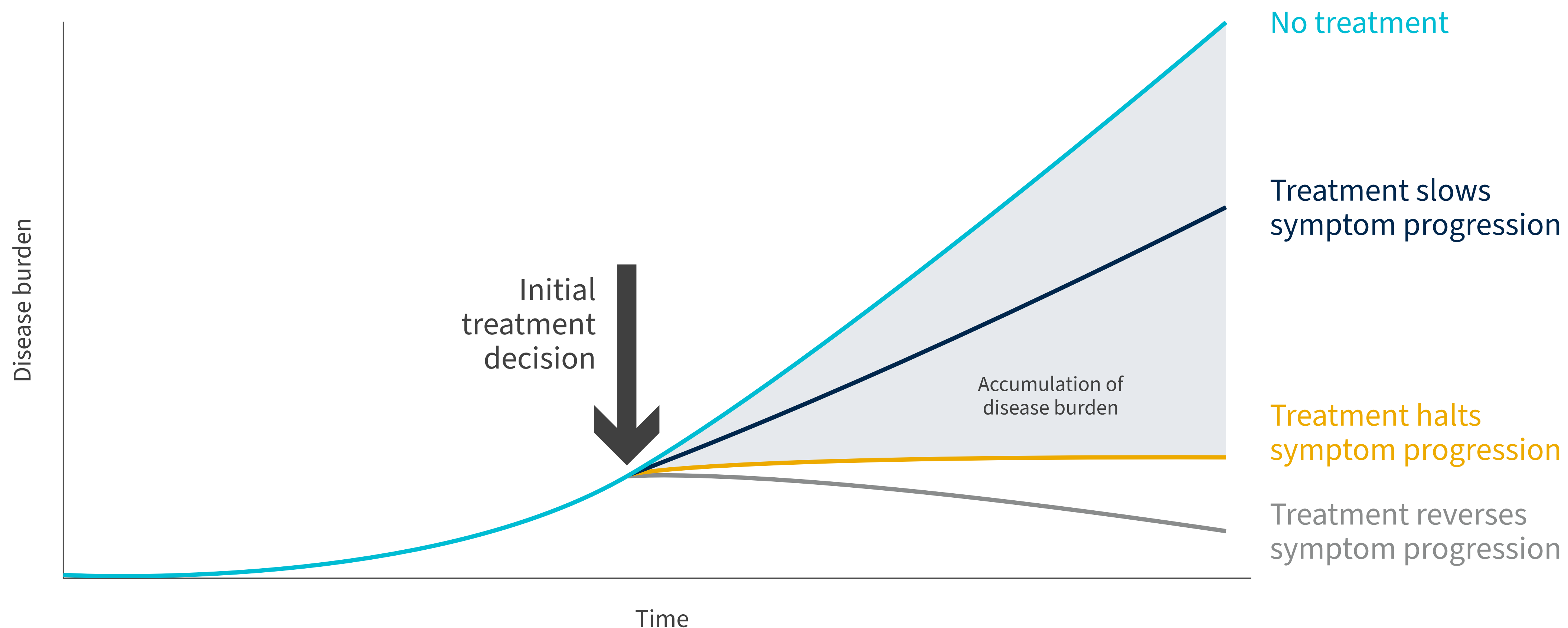
Gastrointestinal disturbances
(i.e., vomiting, alternating diarrhea and constipation, or unintentional weight loss)?

Is there a family history of these symptoms?

It might be time to consider hATTR. Think about offering a genetic test to your patients.¹

References: 1. Conceição I, et al. *J Peripher Nerv Syst* 2016;5-9. 2. Hawkins PN, et al. *Ann Med* 2015;47:625-38.

Initial treatment decisions can determine the disease course in hATTR¹⁻⁶



Schematic illustrating the range of potential treatment outcomes in hATTR

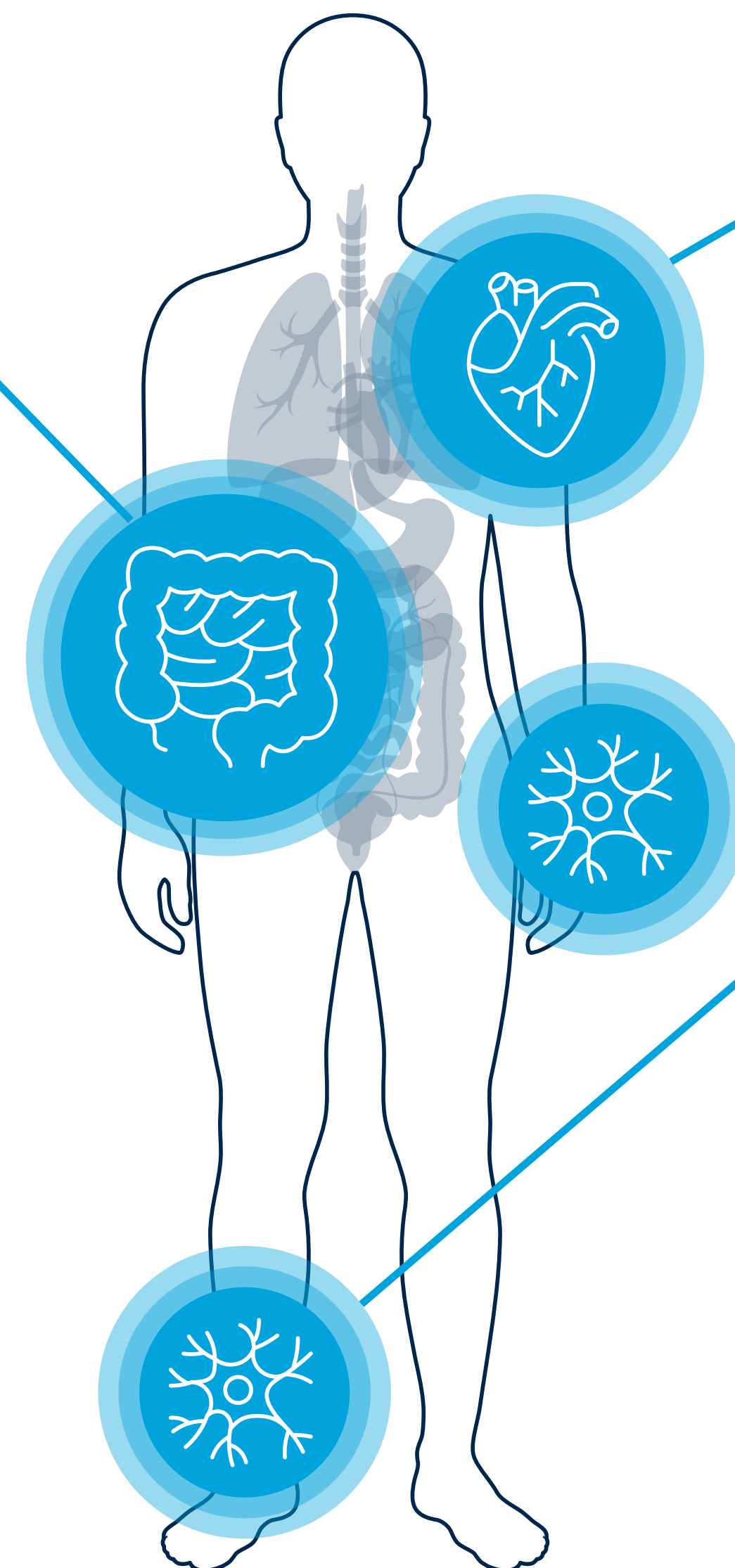
Early diagnosis and timely treatment can change the disease trajectory in hATTR patients.⁴

References: 1. Gertz MA, et al. *Brain Behav* 2019;9:e01371. 2. Gertz M, et al. *BMC Fam Pract* 2020;21:198. 3. Adams D, et al. *Nat Rev Neurol* 2019;15:387-404. 4. Benson MD, et al. *Ther Clin Risk Manag* 2020;16:749-58. 5. Schmidt HH, et al. *Muscle Nerve* 2016;54:353-60. 6. Alcantara M, et al. *Can J Neurol Sci* 2022;49:7-18.

Without treatment, disease burden accumulates rapidly leading to progressive disability and premature death¹⁻³

Autonomic symptoms may appear first – impacting quality of life and threatening survival.^{1,2}

In one long-term observational study (N=52), 41% of deaths were related to wasting.⁴



Cardiomyopathy often develops with time – leading to a progressive decline in physical function, heart failure and death.^{1,3}

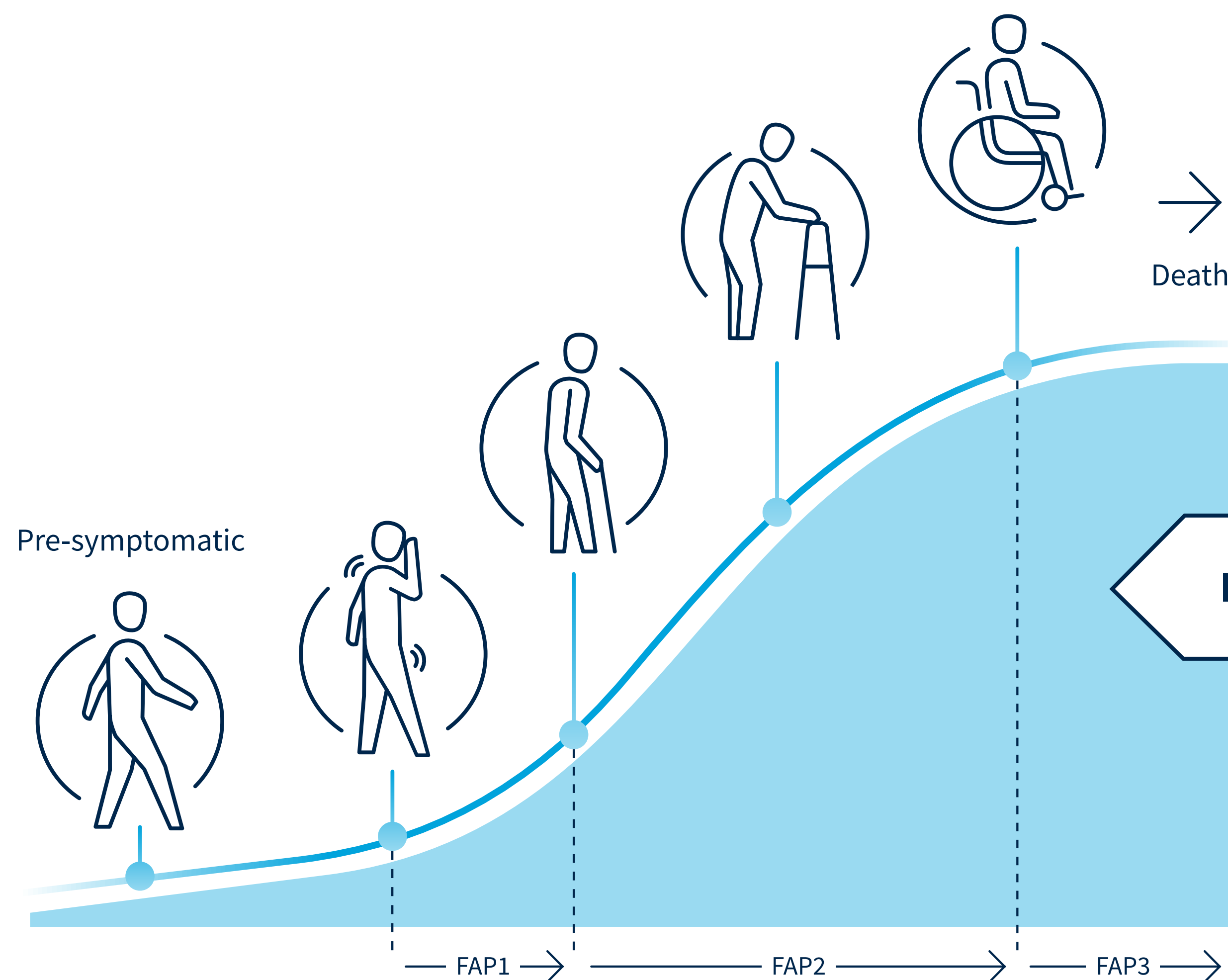
Cardiac denervation can lead to conduction disturbances and arrhythmias, a cause of sudden death in patients.³

Sensory-motor neuropathy can progress quickly, making it increasingly difficult to **walk without assistance.**³

References: 1. Gertz M, et al. *BMC Fam Pract* 2020;21:198.
2. González-Duarte A, et al. *Clin Auton Res* 2019;29:245-51.
3. Adams D, et al. *Nat Rev Neurol* 2019;15:387-404. 4. Gertz MA, et al. *Mayo Clin Proc* 1992;67:428-40.

The systemic amyloid burden contributes to significant disability and mortality in hATTR patients¹

Once symptoms appear, disease progression is rapid¹



Disability within **4-8 years**²

The life expectancy of a patient with hATTR after symptom onset is **~12 years** for early-onset disease and **~7 years** for late-onset disease¹

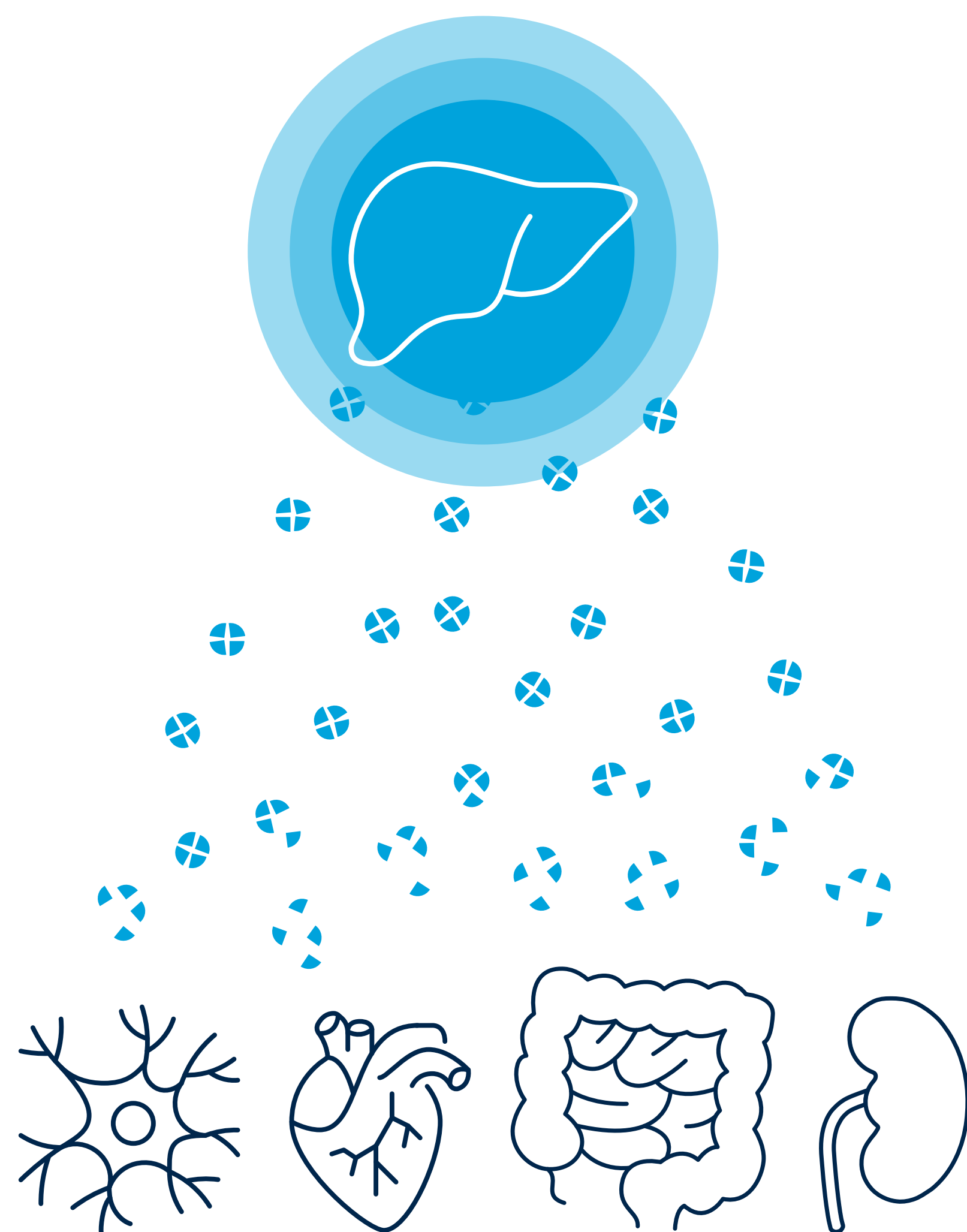
In patients with hATTR, death often results from non-cardiomyopathic manifestations of disease^{3,4}

Figure represents theoretical outcomes and is based on Adams D, et al. 2019 and Adams D, et al. 2013.

FAP1=familial amyloid polyneuropathy stage 1; FAP2=familial amyloid polyneuropathy stage 2; FAP3=familial amyloid polyneuropathy stage 3

References: 1. Adams D, et al. *Nat Rev Neurol* 2019;15:387-404. 2. Adams D. *Ther Adv Neurol Disord* 2013;6:129-39. 3. Gertz MA, et al. *Mayo Clin Proc* 1992;67:428-40. 4. Swiecicki PL, et al. *Amyloid* 2015;22:123-31.

hATTR: A disease that indiscriminately impacts multiple organ systems



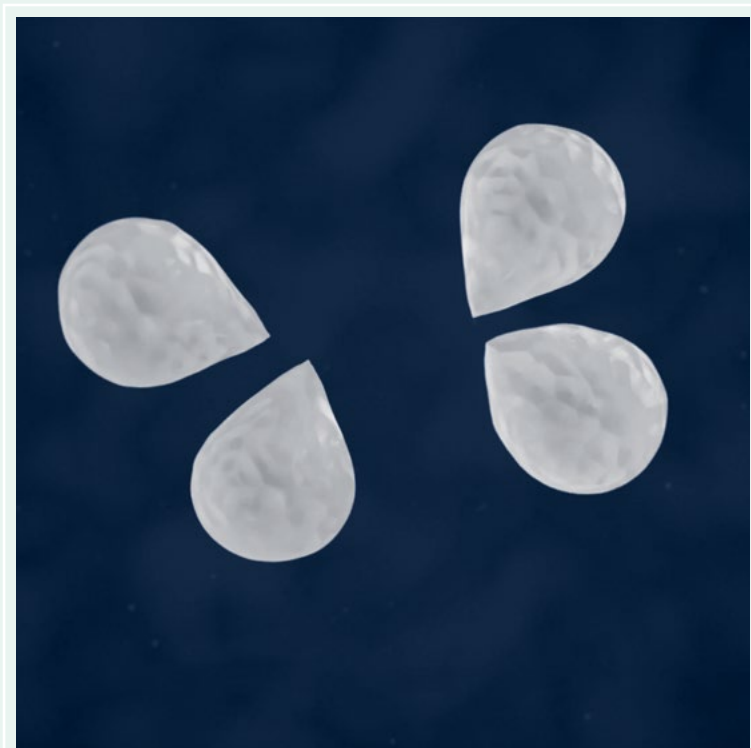
- **Autosomal dominant** disease caused by a mutation in the transthyretin (*TTR*) gene^{1,2}
- **Mutated TTR protein accumulates as amyloid fibrils** in various organs and tissues including the nerves, heart, gut and kidneys^{1,3,4}
- Can cause **progressive dysfunction** and **eventual premature death**¹⁻³

TTR=transthyretin

References: 1. Conceição I, et al. *J Peripher Nerv Syst* 2016;5-9. 2. Ando Y, et al. *Orphanet J Rare Dis* 2013;8:31. 3. Hanna M. *Curr Heart Fail Rep* 2014;11:50-7. 4. Adams D, et al. *Nat Rev Neurol* 2019;15:387-404.

At least three mechanisms lead to the formation of TTR amyloid in hATTR¹⁻⁵

1. TETRAMER DISSOCIATION^{1,6}



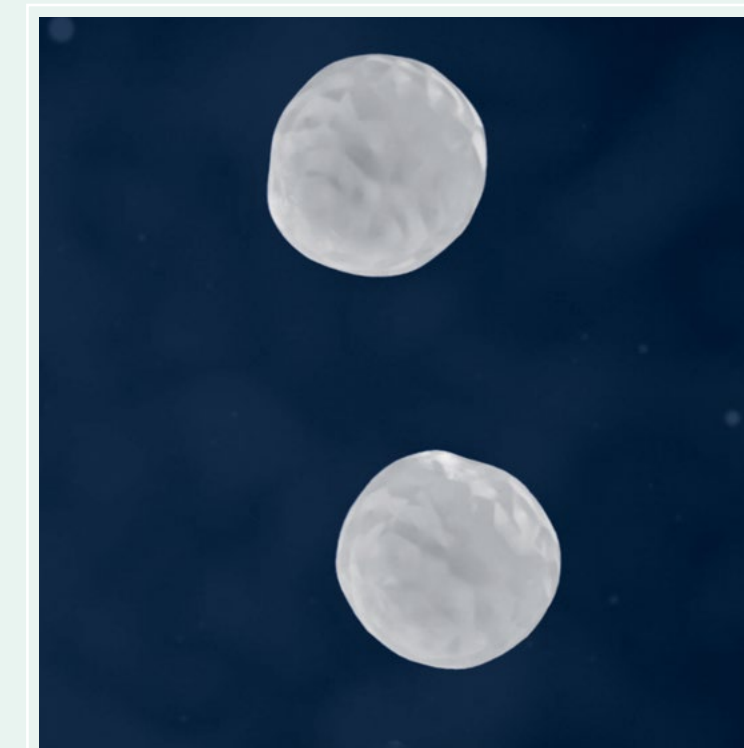
Unstable TTR tetramers dissociate into monomers, which then aggregate into amyloid fibrils.^{1,6,7}

2. PROTEOLYTIC CLEAVAGE AND SHEAR STRESS^{1,3,4,6}



Some TTR variants are cleaved by enzymes – these break into fragments under shear stress (e.g., in the heart).^{3,4,6,8,9}

3. RELEASE OF NON-NATIVE TTR^{2,5}



Deficiencies in quality control mechanisms may result in the release of TTR monomers and oligomers before they form tetramers.^{2,10}

TTR monomers and fragments misfold and aggregate into amyloid fibrils, which causes systemic organ dysfunction.¹

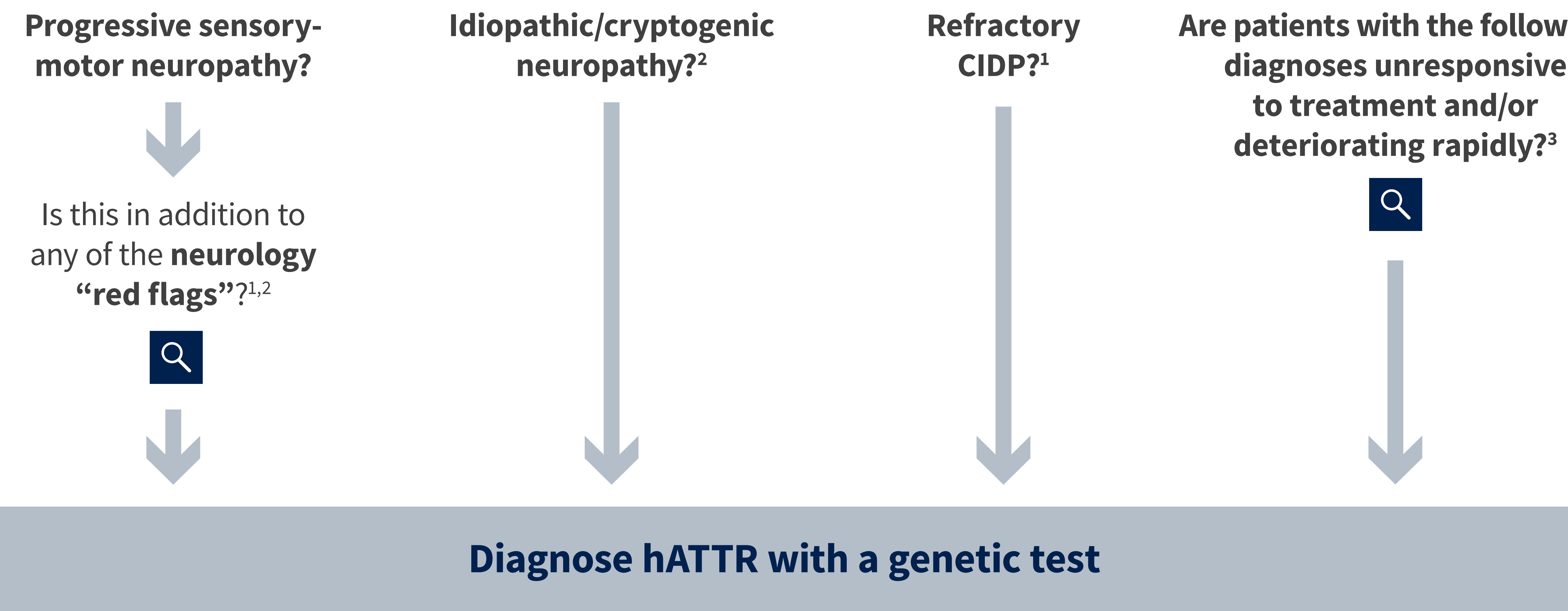
- hATTR starts with the production of **abnormal TTR protein¹**
- Instead of forming stable tetramers, **abnormal TTR protein accumulates as amyloid fibrils in organs throughout the body**, resulting in the multisystem manifestations of the disease^{1,6}
- Once symptoms develop, **progression of hATTR can be rapid¹**

TTR=transthyretin

References: 1. Adams D, et al. *Nat Rev Neurol* 2019;15:387-404. 2. Ibrahim BR, et al. *Cell Mol Life Sci* 2020;77:1421-34. 3. Marcoux J, et al. *EMBO Mol Med* 2015;7:1337-49. 4. Mangione PP, et al. *J Biol Chem* 2018;293:14192-99. 5. Chen JJ, et al. *Cell Chem Biol* 2016;23(10):1282-93. 6. Koike H, Katsuno M. *Biomedicines* 2019;7:11. 7. Ton VK, et al. *Clin Med Insights Cardiol* 2015;8(Suppl 1):39-44. 8. Suhr OB, et al. *J Intern Med* 2017;281:337-47. 9. Mangione PP, et al. *Proc Natl Acad Sci USA* 2014;111:1539-44. 10. Romine IC, Wiseman RL. *Biochem J* 2020;477:1721-32.

Could it be hATTR?

Are you seeing:



CIDP=chronic inflammatory demyelinating polyneuropathy
References: **1.** Conceição I, et al. *J Peripher Nerv Syst* 2016;5-9. **2.** Alcantara M, et al. *Can J Neurol Sci* 2022;49:7-18. **3.** Ando Y, et al. *Orphanet J Rare Dis* 2013;8:31.

Neurology “red flags”



Progressive symmetric sensory-motor neuropathy and at least one of the following:^{1,2}

Bilateral carpal tunnel syndrome (without any other known etiology)	Unexplained weight loss
Cardiovascular complaints (e.g., shortness of breath, edema, palpitations, arrhythmias, previously diagnosed heart failure)	Positive family history
Autonomic dysfunction (e.g., orthostatic hypotension, erectile dysfunction)	Nephropathy (e.g., proteinuria or renal failure)
Gastrointestinal complaints (e.g., diarrhea or constipation, early satiety, nausea, vomiting)	Vitreous opacities

Adapted from Conceição I, et al. 2016.

References: **1.** Conceição I, et al. *J Peripher Nerv Syst* 2016;5-9. **2.** Alcantara M, et al. *Can J Neurol Sci* 2022;49:7-18.

Are patients with the following diagnoses unresponsive to treatment/deteriorating rapidly?¹



CIDP Diabetic polyneuropathy Amyotrophic lateral sclerosis Motor polyradiculoneuropathy Alcoholic neuropathy Carpal tunnel syndrome Idiopathic polyneuropathy Paraneoplastic neuropathy	Motor neuron diseases CMT Amyloid light chain amyloidosis Amyloid A amyloidosis Hypertensive heart disease Hypertrophic cardiomyopathy Fabry's disease Wild-type ATTR amyloidosis
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CIDP=chronic inflammatory demyelinating polyneuropathy; CMT=Charcot-Marie-Tooth disease

Reference: 1. Ando Y, et al. *Orphanet J Rare Dis* 2013;8:31.

Do you have someone like this in your practice?

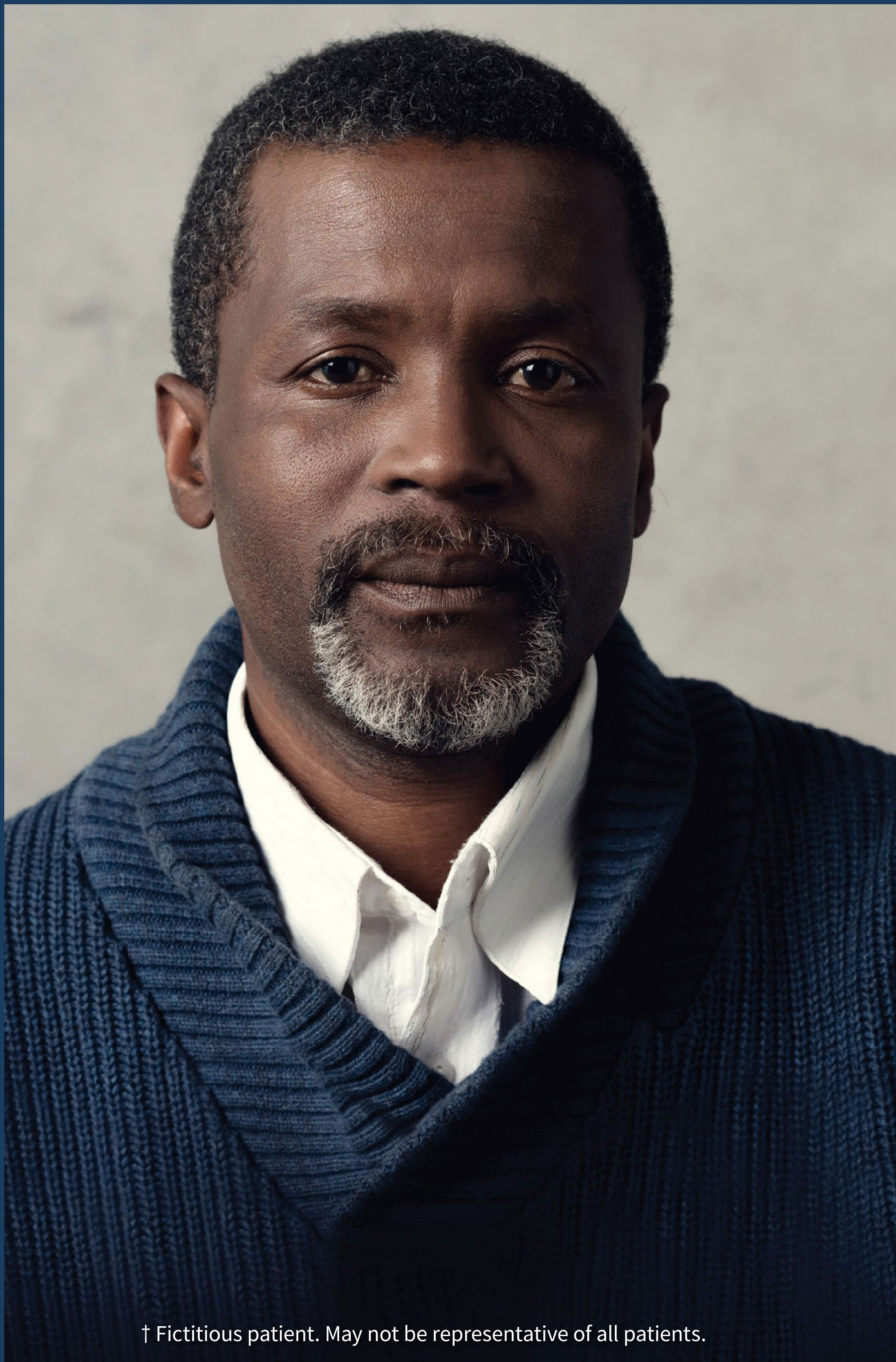


Robert[†]
Sensory-motor plus autonomic neuropathy



Mia[†]
Idiopathic neuropathy

[†] Fictitious patient. May not be representative of all patients.



† Fictitious patient. May not be representative of all patients.

Robert[†]

Sensory-motor plus autonomic neuropathy



Patient history and presentation

- History of bilateral carpal tunnel syndrome, release surgeries in both hands
- Progressive sensory neuropathy that began with neuropathic pain and paresthesia in feet 3 months ago and extended to lower legs
- Referred to gastroenterologist 2 years (alternating diarrhea and constipation)
- Recent onset of early satiety and weight loss

Results of clinical assessments

- Nerve conduction study: reduced motor and sensory responses in hands and feet

Progressive sensory-motor and autonomic neuropathy may suggest hATTR. Confirm hATTR with a genetic test.



† Fictitious patient. May not be representative of all patients.

Mia[†]

Idiopathic neuropathy



Patient history and presentation

- Presented to neurologist 3 months ago for evaluation of numbness and distal weakness; still seeking a diagnosis
- Returned for follow-up due to decline in ambulation over the past month; has started to use a cane when she leaves the house
- History of diabetes and hypertension
- Peripheral edema

Results of clinical assessments

- Nerve conduction study: reduced motor and sensory responses in lower extremities

**Idiopathic neuropathy may suggest hATTR.
Confirm hATTR with a genetic test.**



Alylam® Pharmaceuticals is a biopharmaceutical company developing a potential new class of innovative medicines. We have a core focus on therapeutics toward genetically defined targets for the treatment of serious, life-threatening diseases with limited treatment options for patients and their caregivers.

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