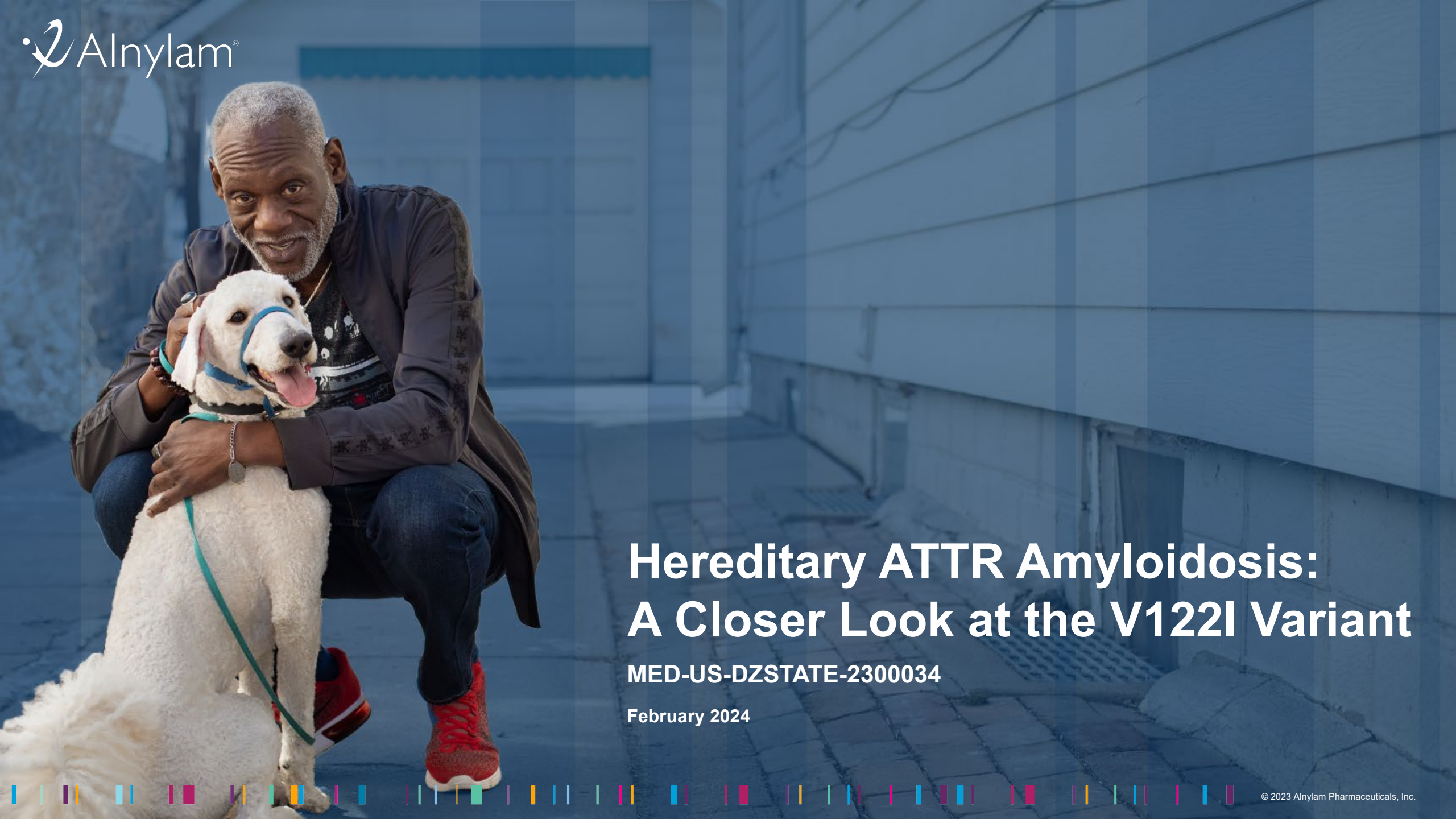

Hereditary ATTR Amyloidosis: A Closer Look at the V122I Variant

MED-US-DZSTATE-2300034

February 2024

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V122I Disease State Deck

- This resource provides information about the V122I variant in hereditary transthyretin-mediated amyloidosis.
- This resource is intended to be viewed in its entirety for educational purposes only 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.

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Objectives

- Provide an overview of transthyretin-mediated (ATTR) amyloidosis
- Review prevalence and prognosis of the V122I variant in hereditary transthyretin-mediated (hATTR) amyloidosis
- Discuss clinical presentation and opportunities for earlier recognition in patients with V122I hATTR amyloidosis
- Discuss diagnosis, management, and monitoring of patients with V122I hATTR amyloidosis

ATTR, transthyretin-mediated; hATTR, hereditary transthyretin-mediated.

Case study*

- **HPI**:
  - MP, a 70-year-old African American male, presents to your cardiology clinic for follow up after being diagnosed with heart failure.
  - MP complains of shortness of breath, fatigue, weakness in hands, and loss of sensation in feet.
- **PMH**:
  - Hypertension
  - Peripheral neuropathy
  - Bilateral carpal tunnel syndrome
- **Family history**:
  - CHF, type 2 diabetes (father)
- **Surgical history**:
  - Bilateral carpal tunnel release (2018)
- **Current medications**:
  - Lisinopril 5 mg PO QD
  - Furosemide 20 mg PO BID
  - Gabapentin 300 mg PO TID
- **Previous medications**:
  - Metoprolol
    - Discontinued due to hypotension, fatigue, and bradycardia
- **Labs**:
  - eGFR: 60 mL/min/1.73m^2
  - NT-proBNP: 2145 pg/mL
  - Troponin T: 0.04 ng/mL
- **Imaging**:
  - Echocardiogram
    - EF: 45%
    - LV wall thickness: 1.8 cm
    - Relative wall thickness: 0.8

*This patient profile was created via a review of published literature and is not an actual patient.

BID, two times daily; CHF, congestive heart failure; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HPI, history of present illness; LV, left ventricular; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PMH, past medical history; PO, by mouth; QD, once daily; TID, three times daily.

Overview of ATTR Amyloidosis and V122I

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One disease, multiple manifestations, driven by TTR amyloid

- An underdiagnosed, rapidly progressive, debilitating, and fatal disease caused by misfolded transthyretin (TTR) protein that accumulates as amyloid deposits in multiple organs and tissues

ATTR amyloidosis	
Hereditary (hATTR) amyloidosis	**Wild-type (wtATTR) amyloidosis**
Inherited	**Non-hereditary**
Variant and wild-type TTR	Wild-type TTR
Multisystem disease that can include sensory, motor, autonomic, and cardiac manifestations	

ATTR, transthyretin-mediated; hATTR, hereditary transthyretin-mediated; TTR, transthyretin; wtATTR, wild-type transthyretin-mediated.

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

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Pathophysiology of ATTR amyloidosis

- Transthyretin (TTR) is a 127-amino acid protein primarily produced in the liver
- Binds and transports serum retinol-binding protein/vitamin A and a minor fraction of serum thyroxine
- Both wild-type and variant TTR tetramers can dissociate, but pathogenic *TTR* variants increase tetramer instability and susceptibility to proteolysis
- Sites of amyloid deposition include the nerves, heart, and the GI tract

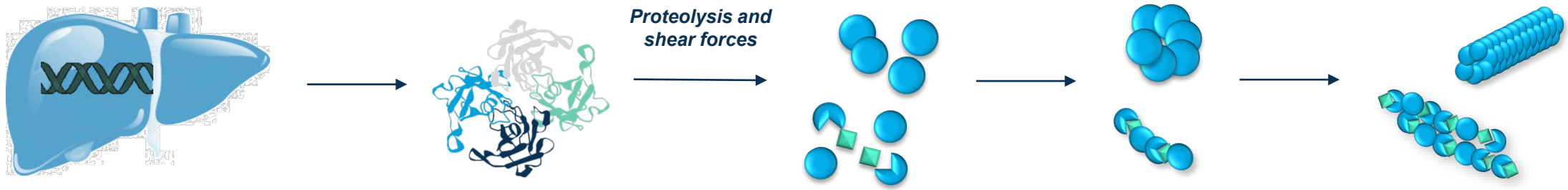

Image adapted from Ando et al. 2022

ATTR, transthyretin-mediated; GI, gastrointestinal; TTR, transthyretin.

Ando et al. *Amyloid.* 2022;29(3):143–55.

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hATTR amyloidosis is an inherited disease where variant carriers demonstrate incomplete and variable penetrance

- Over 130 identified *TTR* variants associated with hATTR amyloidosis[1]
  - Common variants include V30M, V122I, and T60A
- Most common *TTR* variant in the United States is V122I[1,2]
  - Valine-to-isoleucine substitution at position 122 of the protein sequence
  - Also described as Val122Ile, pV142I, p.Val142Ile

Clinical manifestations* of the most common *TTR* variants[3]

Variant	Peripheral Neuropathy	Autonomic Neuropathy	Cardiomyopathy	Gastrointestinal Involvement	Ocular Involvement	Renal Involvement
V30M (early onset)	++	+++	±	++	+	+
V30M (late onset)	+++	+	++	+	+	±
V122I	±	±	+++	±	±	±
T60A	+	+	+++	±	±	±

Note: The number of "+" provides an indication of the likelihood of presence of symptoms, with "±" indicating an unknown likelihood as the symptom is present in some patients and not others.
**Patients may experience clinical manifestations other than those listed above; clinical manifestations may vary by patient.*

hATTR, hereditary transthyretin-mediated; TTR, transthyretin.

1. Kittleson et al. *J Am Coll Cardiol*. 2023;81(11):1076-1126; 2. Maurer et al. *Circ Heart Fail*. 2019;12(9):e006075; 3. Luigetti et al. *Ther Clin Risk Manag*. 2020;16:109-123.

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V122I is most prevalent in patients of African descent

- Genotyping suggests the V122I allele originated in West Africa and was brought to North America via the transatlantic slave trade[1]
- In the US, **~1 in 25 of African Americans** have the V122I variant, corresponding to approximately 1.5 million carriers[2,3]
- The V122I allele is prevalent in up to **1 in 10 African Americans** older than the age of 65 with cardiomyopathy and heart failure[2]

Geographic Distribution of V122I Variant Prevalence

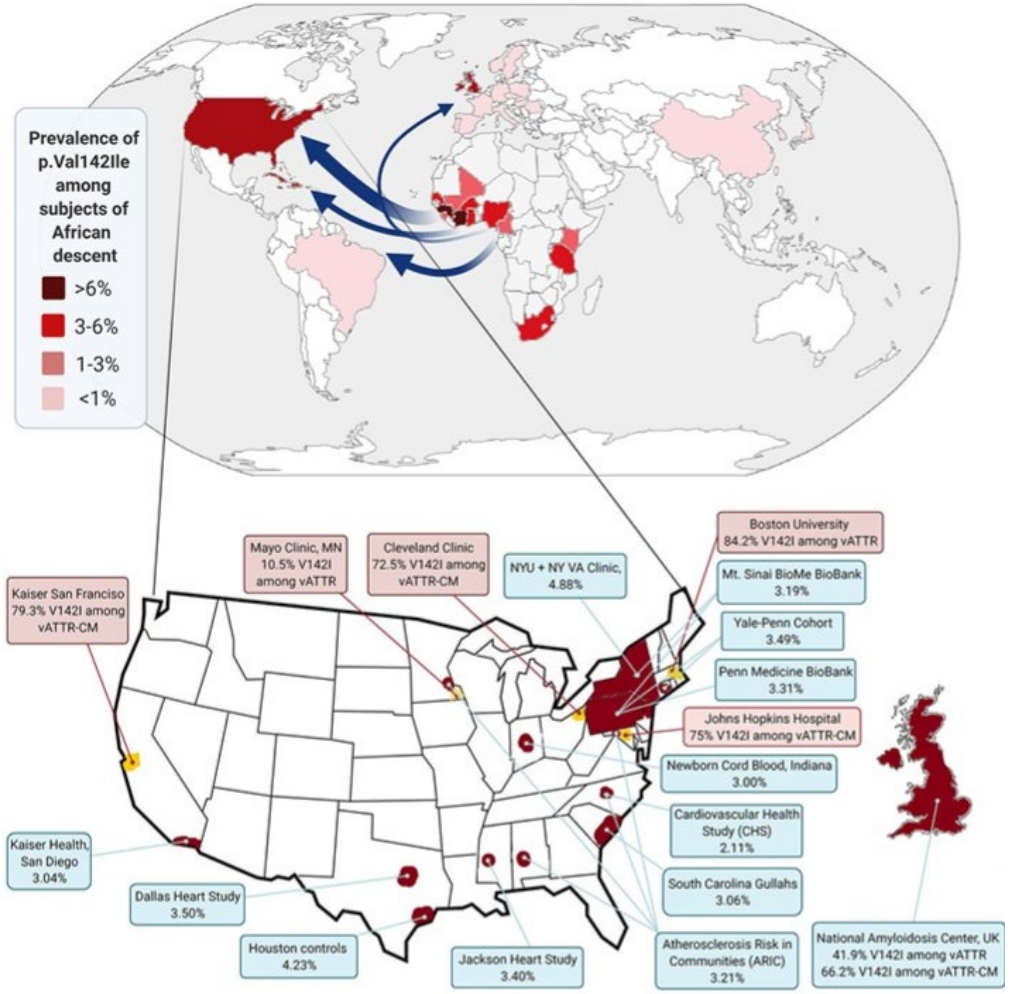

Figure from Chandrashekar et al.[1]

US, United States.

1. Chandrashekar et al. *Circ Genom Precis Med*. 2021;14(5):e003356; 2. Buxbaum and Ruberg. *Genet Med*. 2017;19(7):733-742; 3. Madhani et al. *J Am Heart Assoc*. 2023;12(15):e028973.

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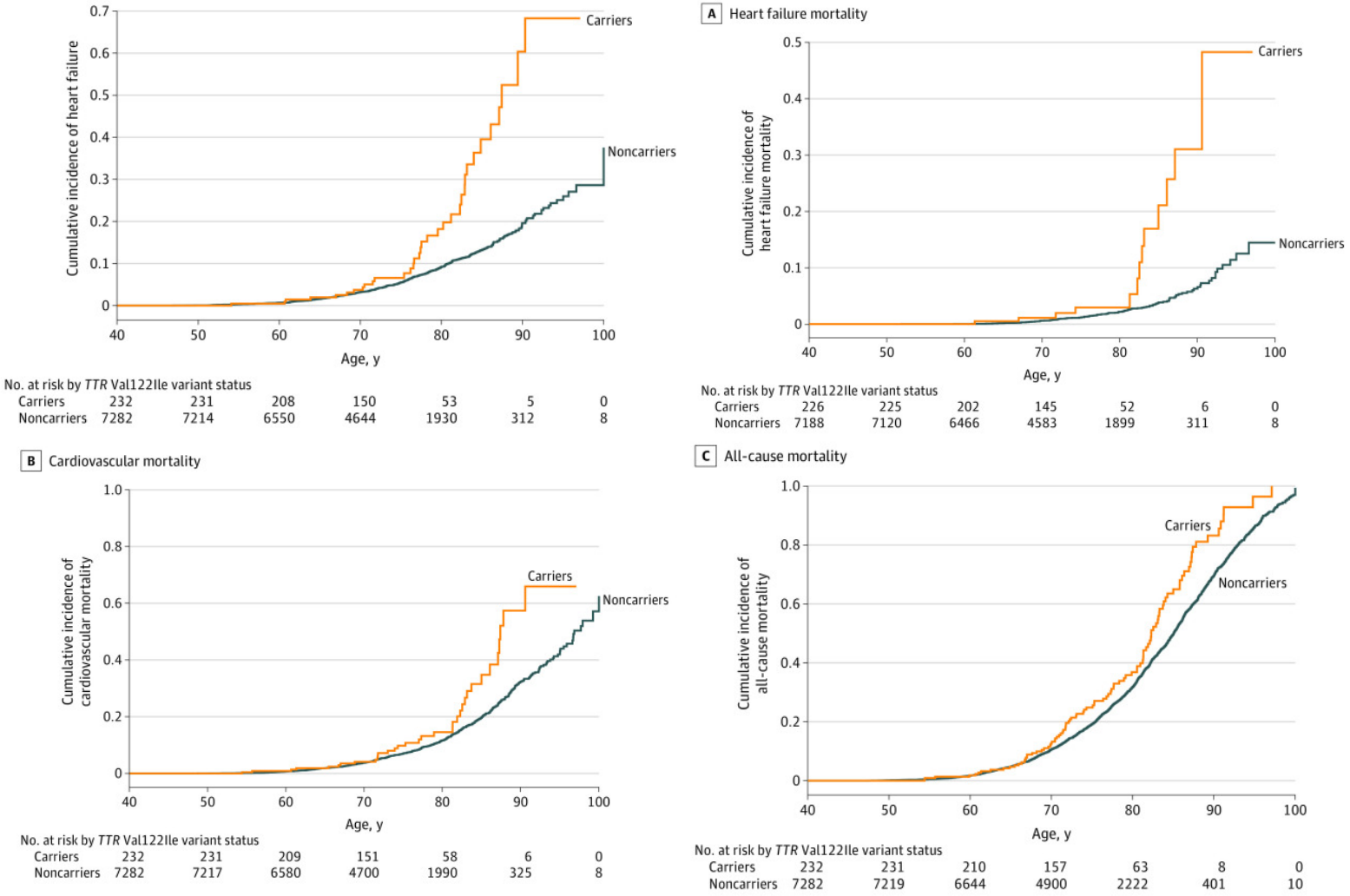
Carriers of the V122I variant have an increased risk of heart failure and mortality

- Retrospective cohort study of Black individuals in the US enrolled in REGARDS (Reasons for Geographic and Racial Differences in Stroke) study (n=7514)*
- V122I carriers had significantly higher
  - **HF incidence**: 15.64 vs. 7.16 per 1000 person-years (adjusted HR: 2.43; 95% CI: 1.71-3.46, p<.001)
  - **HF mortality**: 6.11 vs. 1.85 per 1000 person-years (adjusted HR: 4.19; 95% CI: 2.33-7.54; p<.001)
- Individuals with suspected HF at baseline were excluded, potentially underestimating the disease burden of V122I carriers

Risk of HF Incidence, HF Mortality, CV Mortality, and All-Cause Mortality Among Black Individuals



*In REGARDS, patients were enrolled at baseline visit (2003-2007) and median follow-up was 11.1 years.
CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; US, United States; y, years.
Parcha et al. *JAMA*. 2022;327(14):1368-1378.

Patients with V122I hATTR amyloidosis experience significant disease burden and worse prognosis compared to others

Study (Year)	Groups compared	NYHA class ≥3 (%)	African American (%)	Median survival (years)	Key study takeaways
Ruberg et al. (2012)	**V122I** Wildtype	**27** 22	**100** 0	**2.1** 3.6	Patients with **V122I** have worse progression of cardiomyopathy
Givens et al. (2013)	**V122I** Wildtype	NR NR	**96** 3	**3** 5.5	**V122I** is associated with earlier onset, more aggressive disease
Olson et al. (2013)	**V122I** T60A V30M	NR NR NR	**86** 0 5	NR NR NR	**V122I** genotype had highest mortality risk when adjusted for age, sex, and left ventricular ejection fraction
Swiecicki et al. (2015)	**V122I** T60A V30M	**60.7** 25 0	**75** 0 2.4	**2.1** 3.2 3.5	**V122I** status can independently predict mortality
Maurer et al. (2016)	**V122I** Wildtype	**55.3** 34	**86.8** 4.2	NR NR	Patients with **V122I** are younger, have greater burden of neurological symptoms, and worse quality of life
Lane et al. (2019)*	**V122I** T60A Wildtype	NR NR NR	NR NR NR	**2.6** 5.8 4.8	Patients with **V122I** had worse cardiac measures, greater decline in quality of life, and poorer survival
Chacko et al. (2020)*	**V122I** T60A Wildtype	**32.5** 11 17	**86.6** 0 5.5	**3** 5 4.8	Patients with **V122I** had poorer cardiac function at time of diagnosis

*UK-based study.

hATTR, hereditary transthyretin-mediated; NR, not recorded; NYHA, New York Heart Association.

Goyal et al. *Heart Fail Rev*. 2021;27(3):849-856.

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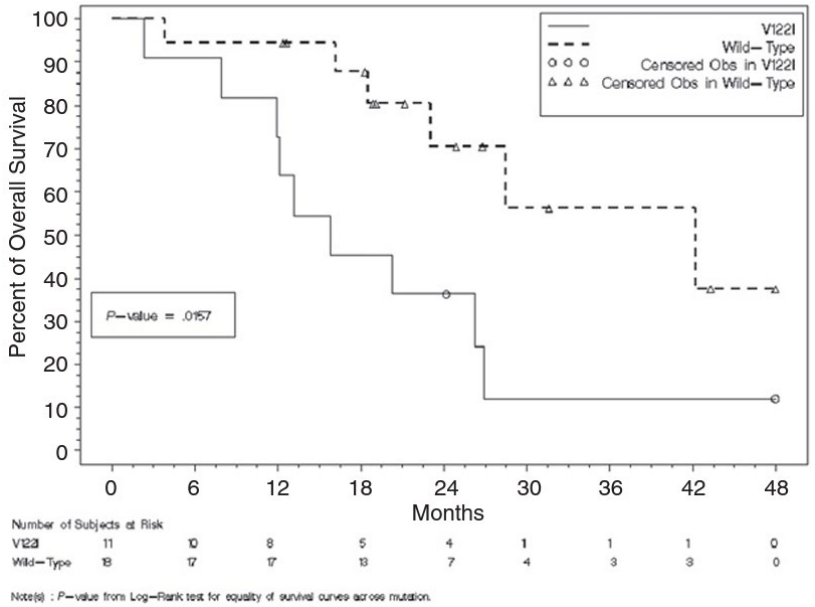
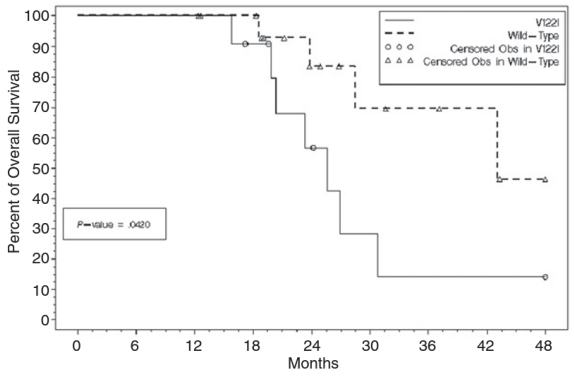
Patients with V122I hATTR amyloidosis have worse progression of cardiomyopathy

- Prospective, observational study of disease progression, morbidity, and mortality in ATTR cardiomyopathy
  - wtATTR (n=18)
  - V122I hATTR (n=11)
- No differences in clinical characteristics between groups at baseline*
  - Mean (±SD) time from diagnosis to enrollment was 10.4 ± 11.9 months
- After 15.5 ± 8 months, patients with V122I hATTR amyloidosis experienced significantly higher:
  - CV hospitalization (64% vs 28%, p=.02)
  - Mortality (73% vs 22%, p=.03)
- Short study duration and small cohort size may limit interpretation of findings, including statistical power

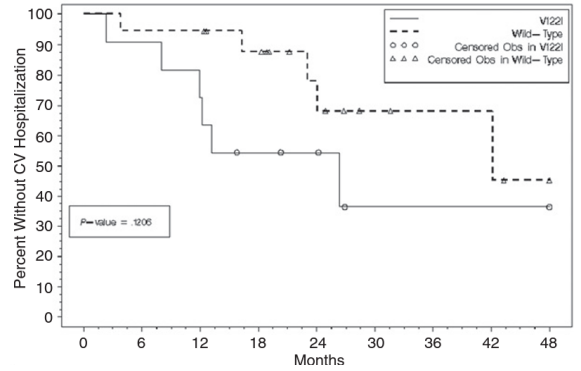
Death or CV Hospitalization



Overall Survival



Freedom from CV Hospitalization



*Mean (±SD) age at enrollment was 76 ± 6 years for wtATTR and 71 ± 5 years for V122I hATTR.

ATTR, transthyretin-mediated; CV, cardiovascular; hATTR, hereditary transthyretin-mediated; SD, standard deviation; wtATTR, wild-type transthyretin-mediated.

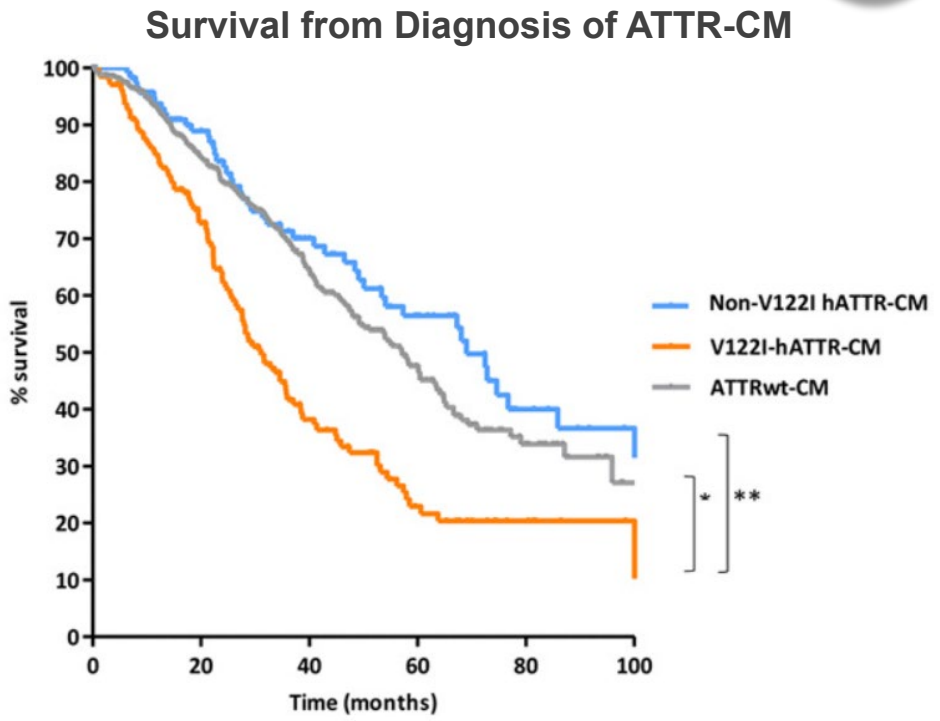
Ruberg et al. *Am Heart J*. 2012;164(2):222-228.e1.

Patients with V122I hATTR amyloidosis have worse cardiac measures, greater decline in quality of life, and poorer survival

- Prospective, observational study of patients with ATTR amyloidosis with cardiomyopathy at the UK National Amyloidosis Center (2000-2017)
  - wtATTR (n=711)
  - V122I hATTR (n=205)
  - Non-V122I hATTR (n=118)

- Compared with other subgroups, patients with V122I hATTR cardiomyopathy had:
  - Worse functional impairment (p<.001)†,a
  - Worse cardiac disease (p<.001)†,b
  - Greater decline in patient-reported quality of life between 12 and 36 months[c]
  - Worse survival (p<.001)

- Sensitive echocardiographic parameters (longitudinal strain, myocardial contraction fraction, relative wall thickness) were not reported



Numbers at risk

Non-V122I-hATTR	118	87	52	34	14	7
V122I-hATTR	205	122	42	18	7	3
ATTRwt	711	415	188	76	24	2

*p<.0001; **p<.0001.

†At diagnosis.

[a] Measured by 6-minute walk test; [b] Measured by biomarkers, echocardiogram; [c] Measured by Kansas City Cardiomyopathy Questionnaire.

ATTR, transthyretin-mediated; hATTR, hereditary transthyretin-mediated; UK, United Kingdom; wtATTR, wild-type transthyretin-mediated.

Lane et al. *Circulation*. 2019;140(1):16-26.

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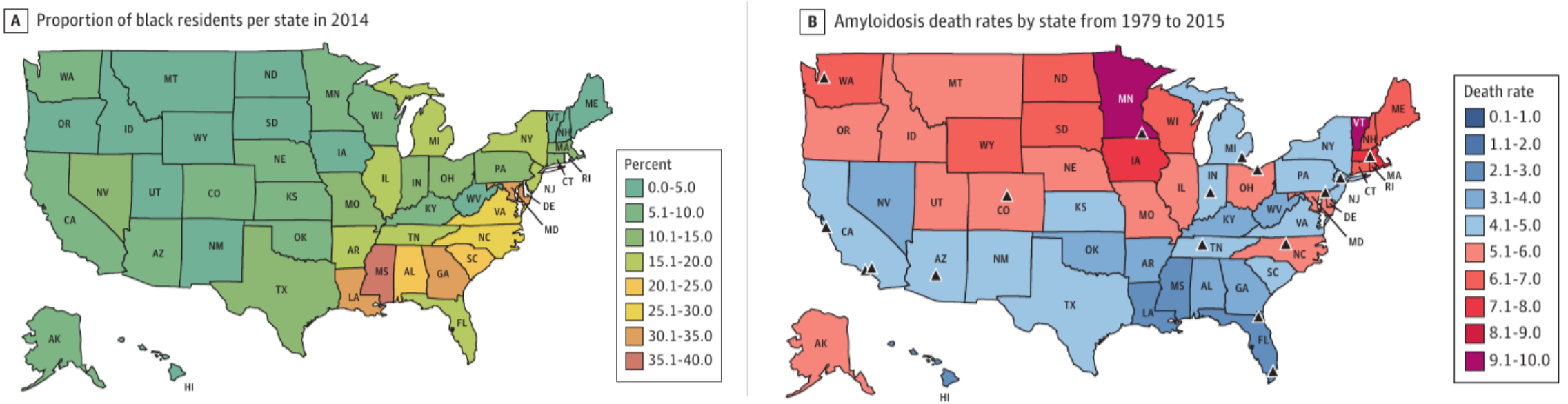
Potential underdiagnosis of cardiac amyloidosis in the US based on a cohort study of death certificate data from 1979 to 2015

- **Black men had the highest reported age-adjusted amyloidosis mortality rate from 1999-2015 at 12.36 per 1,000,000,** which was nearly twice the rate for white men (6.2 per 1,000,000)
- States with higher proportions of black residents were not found to have higher amyloidosis mortality rates, despite black individuals being overrepresented in amyloidosis mortality, suggesting underdiagnosis of cardiac amyloidosis in these regions



US, United States.

Alexander et al. *JAMA Cardiol*. 2018;3(9):865–70.

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II Clinical Presentation

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Awareness of constellation of signs and symptoms can lead to earlier recognition and diagnosis[1,2]

Cardiac

Clinical
- Fatigue
- Family history of HF
- HF symptoms

Electrical
- Atrial fibrillation
- Conduction system disease/pacemaker
- Pseudoinfarct pattern
- Discordant QRS voltage for degree of increased LV wall thickness on imaging

Imaging
- Increased LV wall thickness
- Abnormal longitudinal strain with apical sparing
- Late gadolinium enhancement on CMRI with increased ECV

Labs
- Persistent low-level troponin elevation
- Elevated NT-proBNP

Musculoskeletal

- Bilateral carpal tunnel syndrome
- Lumbar/cervical spine stenosis
- Spontaneous biceps tendon rupture
- Hip or knee replacement

Sensory/motor neuropathy

- Family history of neuropathy
- Peripheral neuropathy
- Muscle weakness
- Difficulty walking, falls

Autonomic neuropathy

- Orthostatic hypotension, intolerance to blood pressure medications
- Chronic diarrhea, constipation, and/or weight loss
- Erectile dysfunction
- Urinary incontinence

CMRI, cardiac magnetic resonance imaging; ECV, extracellular volume fraction; HF, heart failure; LV, left ventricular; NT-proBNP, N-terminal prohormone of brain natriuretic peptide.

1. Nativi-Nicolau et al. *Heart Fail Rev*. 2022;27(3):785-793; 2. Kittleson et al. *J Am Coll Cardiol*. 2023;81(11):1076-1126.

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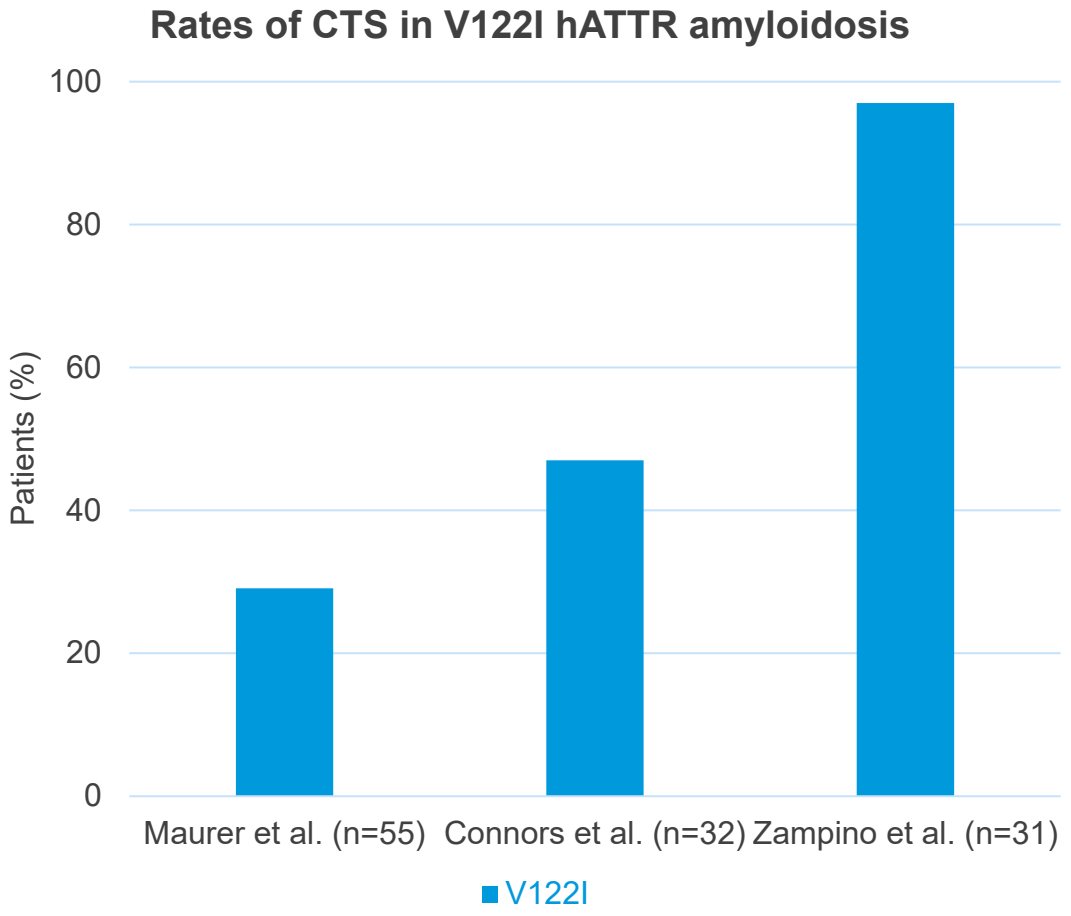
A history of carpal tunnel syndrome (CTS) in African American patients may be a red flag for hATTR amyloidosis

- CTS and/or a history of carpal tunnel release surgery may be an early sign of ATTR amyloidosis[1-3]
- In Zampino et al., CTS preceded hATTR amyloidosis diagnosis by more than 7 years in 30% of V122I patients[3,a]
- Small sample size may limit study interpretation



[a]Retrospective case series of newly diagnosed patients with hATTR amyloidosis (n=31) between 2008 and 2020.

ATTR, transthyretin-mediated; CTS, carpal tunnel syndrome; hATTR, hereditary transthyretin-mediated; TTR, transthyretin.

1. Maurer et al. *J Am Coll Cardiol*. 2016;68(2):161-172; 2. Connors et al. *Am Heart J*. 2009;158(4):607-614; 3. Zampino et al. *Neurology*. 2023;100(19):e2036-e2044.

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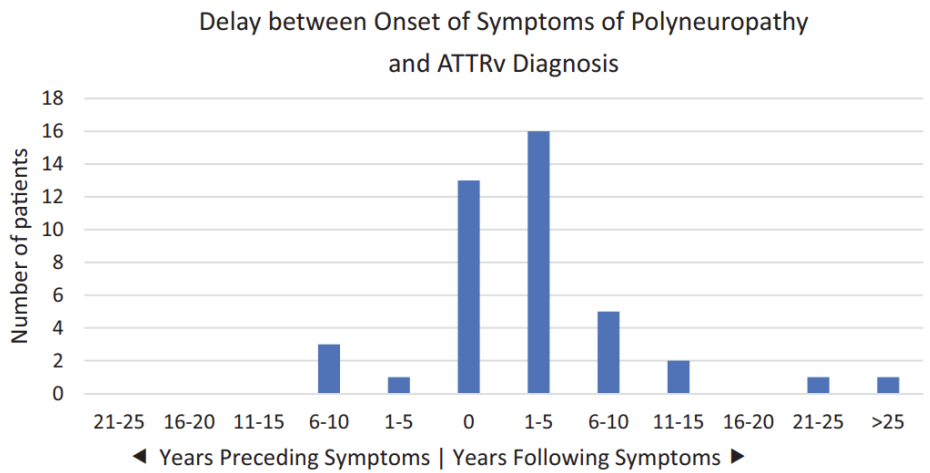
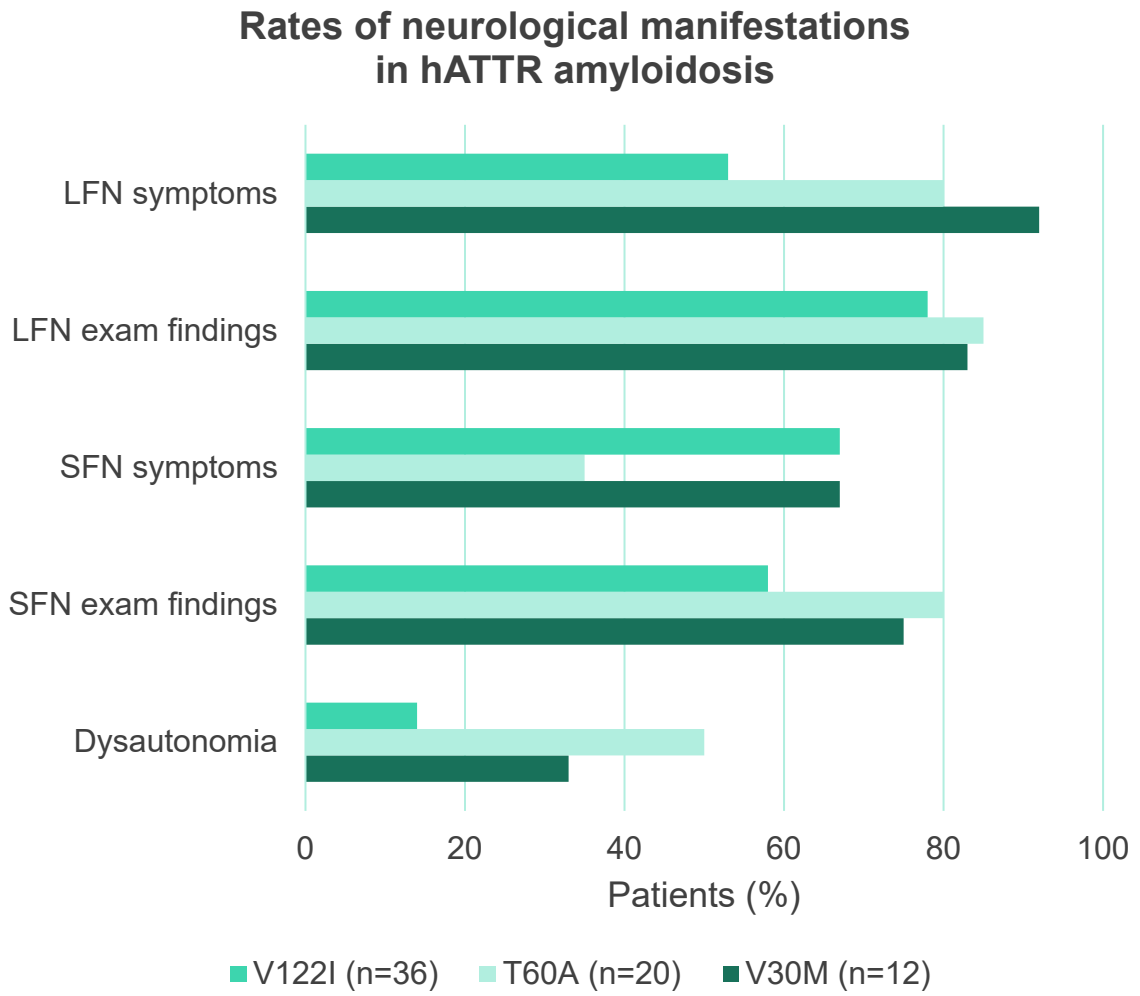
Many patients with V122I hATTR amyloidosis experience symptoms of polyneuropathy

- Retrospective single-center study of patients with hATTR amyloidosis (n=92, 39% V122I)
- Among patients with the V122I variant, 53% had large fiber neuropathy (LFN) symptoms
  - 42% of patients with LFN symptoms did not have signs of cardiac involvement

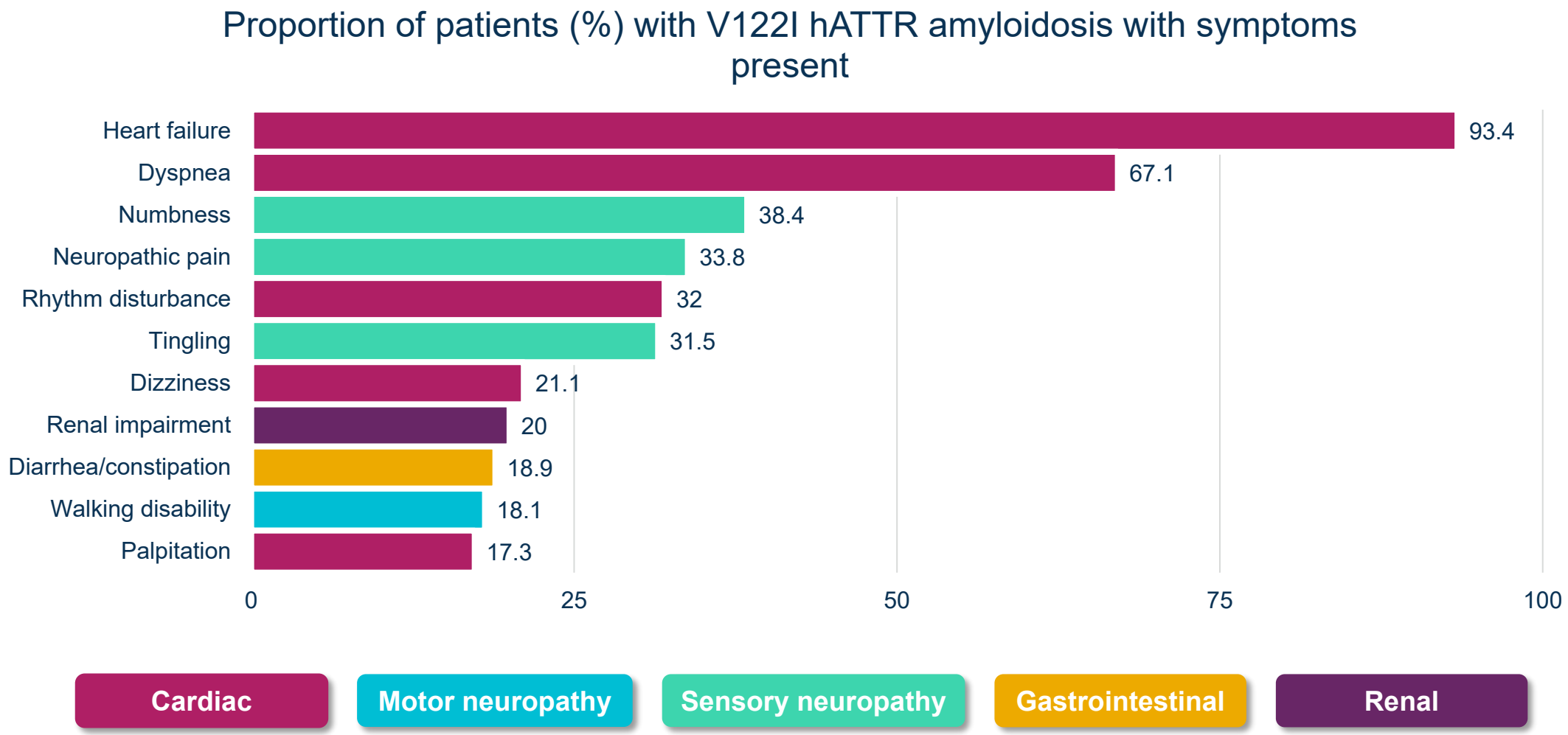




hATTR, hereditary transthyretin-mediated; LFN, large fiber neuropathy; SFN, small fiber neuropathy.

Kaku et al. *Amyloid*. 2022;29(3):184-189.

THAOS: Patients with V122I hATTR amyloidosis with cardiac and extracardiac symptoms



hATTR, hereditary transthyretin-mediated; THAOS, The Transthyretin Amyloid Outcome Survey.

Maurer et al. *J Am Coll Cardiol*. 2016;68(2):161-172.

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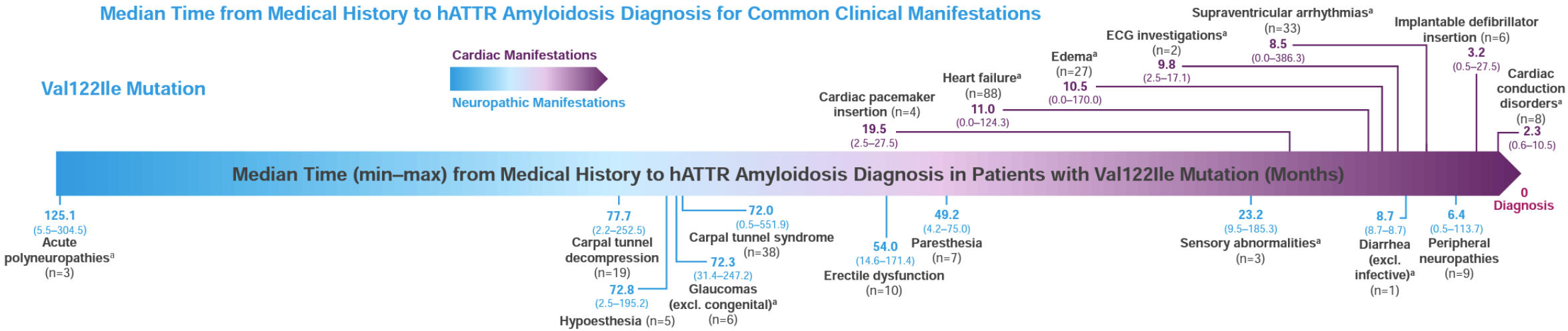
Extracardiac symptoms may precede or coincide with cardiomyopathy

- Among patients with hATTR amyloidosis with cardiomyopathy, symptoms of polyneuropathy were found in more than half based on clinical evaluation and analysis of medical history

- Multisystem disease assessment and early clinical suspicion can help identify patients prior to greater disease burden



hATTR, hereditary transthyretin-mediated.

Grogan et al. Poster presented at: Heart Failure Society of America (HFSA), September 13-16, 2019; Philadelphia, PA.

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Early diagnosis requires awareness of extracardiac symptoms

Atypical presentations of seven male patients with the V122I variant				
Age (years)	**Initial presentation to neurologist**	**Initial diagnosis / Misdiagnosis**	**Cardiac involvement**	**Approximate time from symptom onset to diagnosis**
74	Constipation and bloating Sensory symptoms in hands and feet (numbness)	Idiopathic sensorimotor axonal neuropathy	Shortness of breath CHF	8 years
65	Sensory symptoms in hands and feet (numbness and burning pain)	Idiopathic small-fiber neuropathy	Shortness of breath CHF	10 years
66	Sensory symptoms in hands and feet Lower-extremity weakness	Idiopathic sensorimotor axonal neuropathy	Shortness of breath left ventricular hypertrophy	4 years
58	Sensory symptoms in hands and feet (burning pain) Bilateral carpal tunnel syndrome	Small-fiber neuropathy	Shortness of breath HFpEF	5 years
70	Sensory symptoms in hands and feet Muscle weakness Postural light headedness	Idiopathic sensory and autonomic neuropathy	Shortness of breath CHF and right and left cardiac hypertrophy	5 years
76	Quads atrophy Lower extremities weakness Sensory symptoms in feet	Myopathy and peripheral neuropathy	Shortness of breath CHF and right and left cardiac hypertrophy	10 years
70	Sensory symptoms in hands and feet Postural intolerance	Autonomic and peripheral neuropathy	Shortness of breath CHF and right and left cardiac hypertrophy	3 years

Cardiovascular manifestations | Musculoskeletal manifestations | Sensory/motor manifestations | Autonomic manifestations

CHF, congestive heart failure; HFpEF, heart failure with preserved ejection fraction.

Hussain. *J Clin Neuromuscul Dis*. 2021;23(1):7-17.

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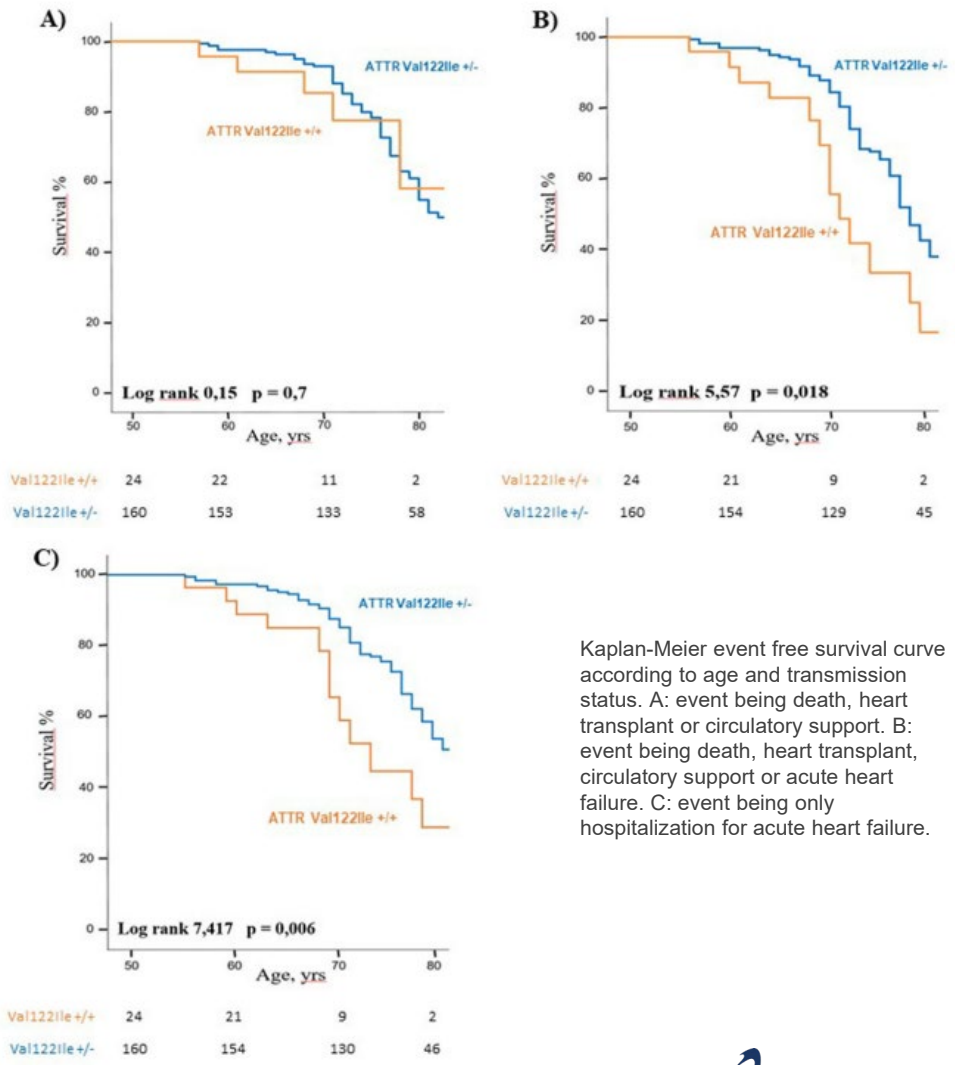
Onset of hATTR symptoms may occur earlier in homozygotes compared to heterozygotes

- Observational, retrospective study of patients with V122I hATTR amyloidosis conducted from 2009 to 2021
- Observed homozygous frequency was 13%
- The following occurred significantly earlier in homozygotes compared with heterozygotes:
  - Median age at diagnosis: 67 [63–71] years vs. 76 [70–79] years, p<.001
  - Age at first cardiac symptom: 66 [61–71] years vs. 74 [68–78] years, p<.001
  - **Age at first extracardiac symptom**: 59 [52–70] years vs. 69 [62–75] years, p=.003
- Disease penetrance is significantly higher among V122I homozygous individuals
- Individuals with positive genetic test results should have regular follow-up prior to development of symptoms and should be made aware of “red flag” symptoms
- Study limitation: small number of homozygotes (n=24) and short follow-up (17 months)

Kaplan-Meier Event Free Survival Curves According to Age and Transmission Status



Kaplan-Meier event free survival curve according to age and transmission status. A: event being death, heart transplant or circulatory support. B: event being death, heart transplant, circulatory support or acute heart failure. C: event being only hospitalization for acute heart failure.

hATTR, hereditary transthyretin-mediated.

Albenque et al. *Amyloid*. 2023;1-9.

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Which ATTR amyloidosis "red flags" are present in this patient?*

- **HPI**:
  - MP, a 70-year-old African American male, presents to your cardiology clinic for follow up after being diagnosed with heart failure.
  - MP complains of shortness of breath, fatigue, weakness in hands, and loss of sensation in feet.
- **PMH**:
  - Hypertension
  - Peripheral neuropathy
  - Bilateral carpal tunnel syndrome
- **Family history**:
  - CHF, type 2 diabetes (father)
- **Surgical history**:
  - Bilateral carpal tunnel release (2018)
- **Current medications**:
  - Lisinopril 5 mg PO QD
  - Furosemide 20 mg PO BID
  - Gabapentin 300 mg PO TID
- **Previous medications**:
  - Metoprolol
    - Discontinued due to hypotension, fatigue, and bradycardia
- **Labs**:
  - eGFR: 60 mL/min/1.73m^2
  - NT-proBNP: 2145 pg/mL
  - Troponin T: 0.04 ng/mL
- **Imaging**:
  - Echocardiogram
    - EF: 45%
    - LV wall thickness: 1.8 cm
    - Relative wall thickness: 0.8

*This patient profile was created via a review of published literature and is not an actual patient.

ATTR; transthyretin-mediated; BID, two times daily; CHF, congestive heart failure; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HPI, history of present illness; LV, left ventricular; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PMH, past medical history; PO, by mouth; QD, once daily; TID, three times daily.

Which ATTR amyloidosis "red flags" are present in this patient?*

- **HPI**:
  - MP, a **70-year-old African American male**, presents to your cardiology clinic for follow up after being diagnosed with **heart failure**.
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  - Hypertension
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II Opportunities for Earlier Recognition

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A score to identify ATTR-CM amyloidosis risk

- Retrospective cohort study of patients with HF (EF ≥40%) and suspected ATTR-CM referred to Mayo Clinic for PYP (n=666) between 2013 and 2020
- Aimed to derive and validate a scoring system to identify patients at increased risk of ATTR-CM
- Score was validated in more diverse cohort with HFpEF referred for PYP (n=66)
  - 37% of patients were African American
- A score of ≥6 had a PPV of 25% in clinically relevant ATTR-CM prevalence (10% of patients with HFpEF) scenarios
- Study limitation: ATTR-CM score derived in patients referred for PYP imaging, risk score may not perform similarly in broad HFpEF population

ATTR-CM Score		
Clinical variable	**Value**	**Points[a]**
Age (y)	If 60-69	+2
	If 70-79	+3
	If ≥80	+4
Sex	Male	+2
Hypertension diagnosis	Present	-1
Ejection fraction	<60%	+1
Posterior wall thickness	≥12 mm	+1
Relative wall thickness	>0.57	+2
Score ≥6 = high risk		
[a]If variable is absent, points = 0		

ATTR-CM, transthyretin-mediated with cardiomyopathy; EF, ejection fraction; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; PPV, positive predictive value; PYP, pyrophosphate; y, years.

Davies et al. *JAMA Cardiol*. 2022;7(10):1036-1044.

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10% of patients undergoing carpal tunnel release surgery were amyloid positive on biopsy

- Prospective study of patients who had carpal tunnel release surgery between 2016 and 2017
- 98 patients enrolled
  - Median age: 68 years
  - 85% had bilateral symptoms
  - 94% white
- **10 patients (10.2%) amyloid-positive on tenosynovial biopsy**
  - 7 ATTR (2 hATTR)
  - 2 AL
  - 1 untyped

Cleveland Clinic amyloidosis algorithm for biopsy during carpal tunnel release

Tier 1

- Male age ≥50 years
- Female age ≥60 years
- Bilateral carpal tunnel symptoms or prior release surgery

Tier 2

- Spinal stenosis
- Biceps tendon rupture
- Atrial fibrillation or flutter (active or previous history)
- Pacemaker
- Congestive heart failure
- Family history of ATTR amyloidosis

TWO characteristics from **Tier 1**

OR

ONE characteristic from Tier 1 *PLUS* any **ONE** from **Tier 2**

↓

Tenosynovial and/or transverse carpal ligament tissue biopsy with Congo red (or Thioflavin-S) staining

Amyloid typing (mass spectroscopy)

If amyloid (+) →

Referral to amyloid expert

AL, light chain; ATTR, transthyretin-mediated; hATTR, hereditary transthyretin-mediated.

Sperry et al. *J Am Coll Cardiol*. 2018;72(17):2040-2050.

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Opportunities for earlier recognition in patient case*

- **Clinical variables from case:**
  - **70-year-old (+3)**
  - **Male (+2)**
  - Hypertension (-1)
  - **EF: 45% (+1)**
  - **LV wall thickness: 1.8 cm (+1)**
  - **Relative wall thickness: 0.8 (+2)**

- **Patient received carpal tunnel release surgery in 2018**
  - If facility still has patient's tissue samples, can perform Congo red staining to determine if they are amyloid-positive[1]

Tier 1[3]
• **Male age ≥50 years**
• Female age ≥60 years
• **Bilateral carpal tunnel symptoms or prior release surgery**

ATTR-CM Score[2]		
Clinical variable	**Value**	**Points[a]**
Age (y)	If 60-69	
	If 70-79	**+3**
	If ≥80	
Sex	**Male**	**+2**
Hypertension diagnosis	Present	-1
Ejection fraction	**<60%**	**+1**
Posterior wall thickness	**≥12 mm**	**+1**
Relative wall thickness	**>0.57**	**+2**
Patient score = 8 (high risk)		
[a] If variable is absent, points = 0		

*This patient profile was created via a review of published literature and is not an actual patient.

EF, ejection fraction; LV, left ventricular; y, years.

1. Soper et al. *J Pers Med*. 2021;11(1):49; 2. Davies et al. *JAMA Cardiol*. 2022;7(10):1036-1044; 3. Sperry et al. *J Am Coll Cardiol*. 2018;72(17):2040-2050.

Diagnosis

This information is provided as a reference resource and should not substitute for clinical judgment.

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ACC 2023 neurologic evaluation for ATTR amyloidosis

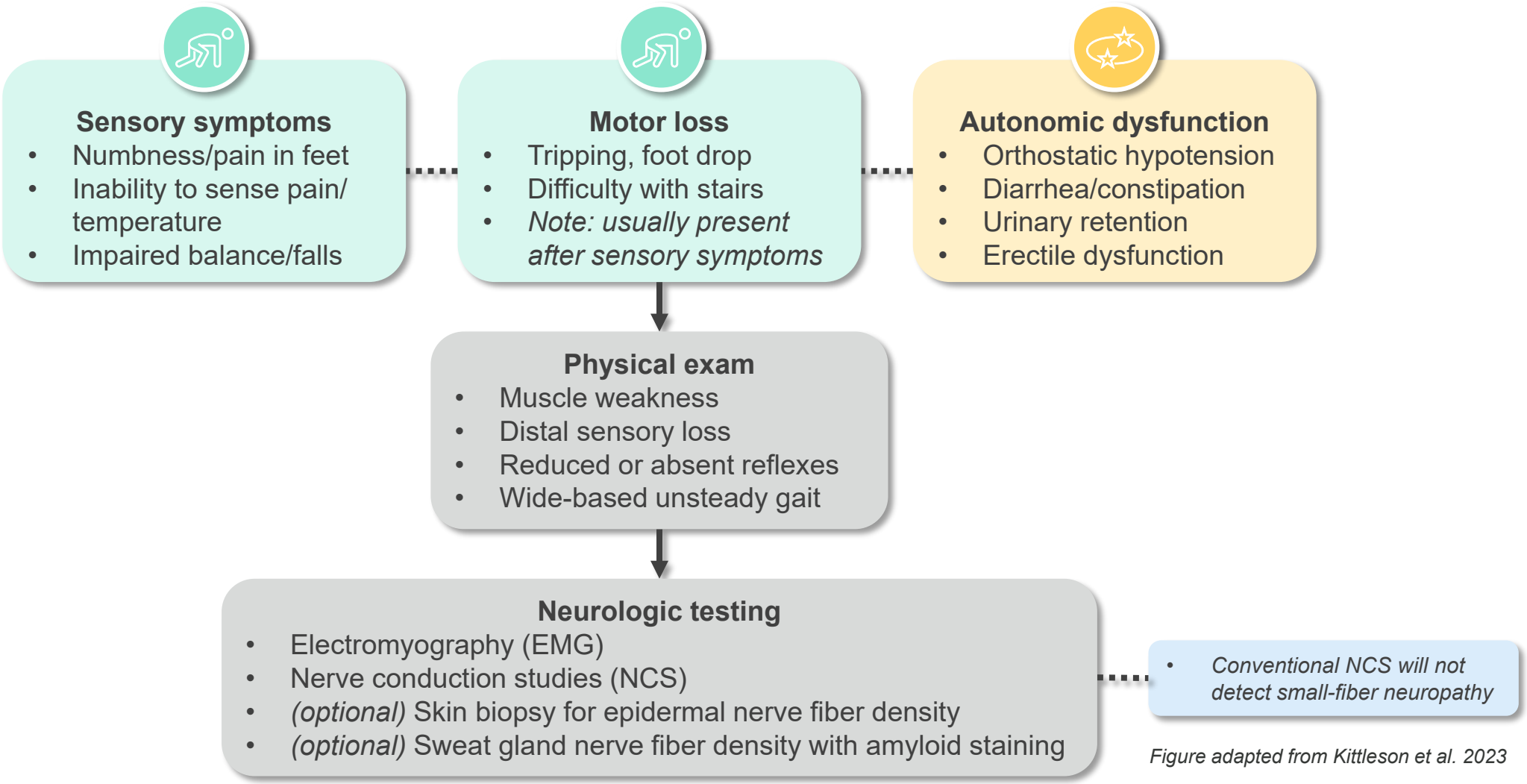

Figure adapted from Kittleson et al. 2023

ACC, American College of Cardiology; ATTR, transthyretin-mediated; BP, blood pressure; DBP, diastolic blood pressure; NCS, nerve conduction study; OH, orthostatic hypotension; SBP, systolic blood pressure.

Kittleson et al. *J Am Coll Cardiol.* 2023;81(11):1076-1126.

ACC 2023 diagnostic algorithm for ATTR-CM amyloidosis

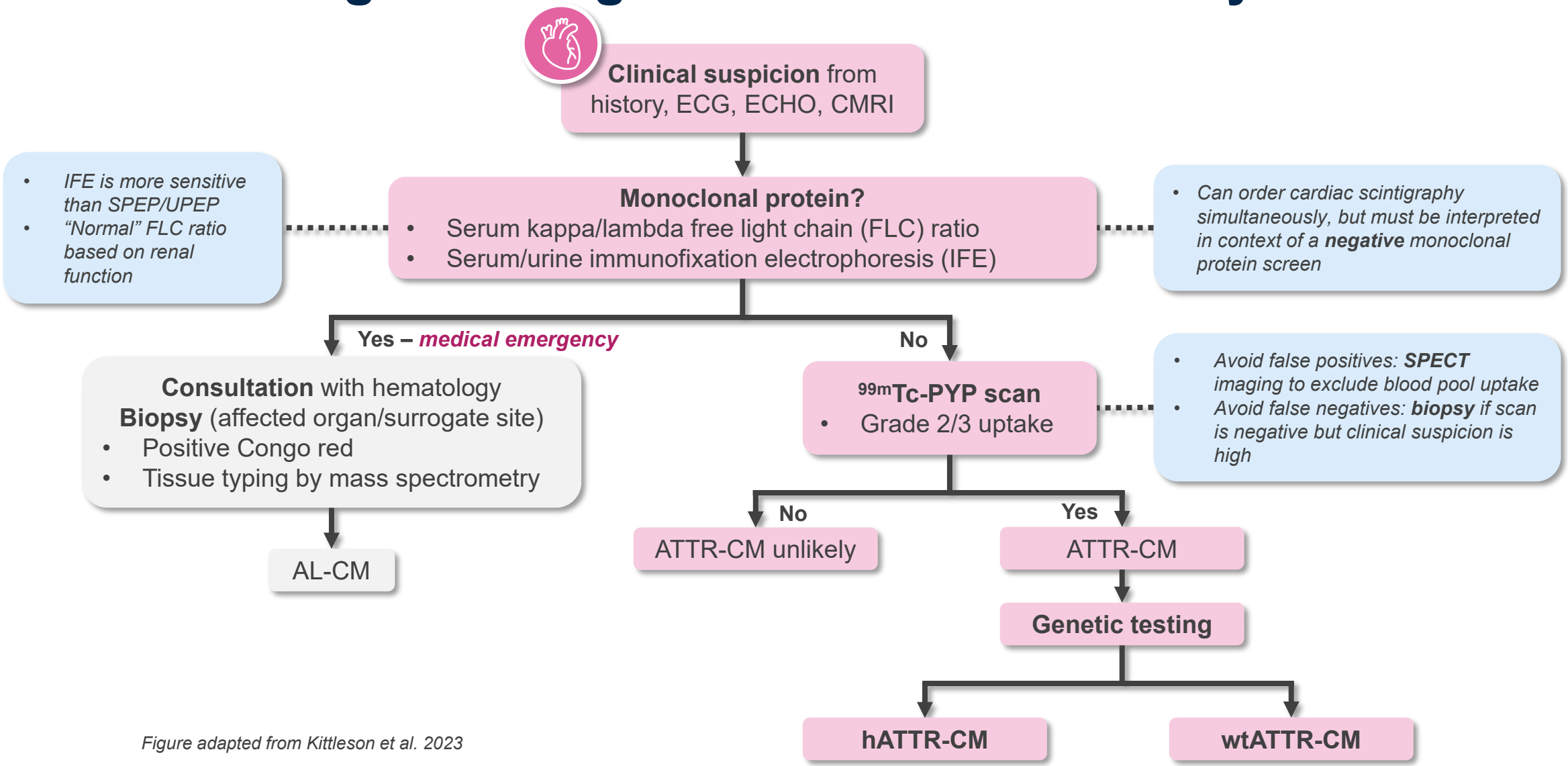

Figure adapted from Kittleson et al. 2023

^{99m}Tc-PYP, technetium-^{99m}-pyrophosphate; ACC, American College of Cardiology; AL-CM, amyloid monoclonal immunoglobulin light chain cardiomyopathy; ATTR-CM, transthyretin-mediated cardiomyopathy; CMRI, cardiac magnetic resonance imaging; ECG, electrocardiogram; ECHO, echocardiogram; FLC, free light chain; hATTR-CM, hereditary transthyretin-mediated cardiomyopathy; IFE, immunofixation electrophoresis; SPECT, single-photon emission computed tomography; SPEP/UPEP, serum/urine protein electrophoresis; wtATTR-CM, wild-type transthyretin-mediated cardiomyopathy.

Kittleson et al. *J Am Coll Cardiol.* 2023;81(11):1076-1126.

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Ruling out AL by looking for clonal plasma cells: A 2-step process[1]

Step 1: Assess for clonality by measuring plasma cell byproducts

To measure **clonal antibody** (e.g., IgG-λ), use **serum** protein electrophoresis with immunofixation (SPIE)

Preferred test because clonal antibodies are commonly present at higher concentration in the serum than are clonal light chains

+

To measure **clonal light chain** (e.g., λ light chain), use **urine** protein electrophoresis with immunofixation (UPIE)

Preferred test because light chains are concentrated in the urine; UPIE is used primarily to identify clonal light chains

Step 2: Evaluate the ratio of κ:λ free light chain (FLC) based on renal function*

GFR (ml/min/1.73 m^2)	>60	40-60	<40
Main determinant of κ:λ FLC ratio	Renal clearance	Renal clearance and bone marrow production	Bone marrow production
"Normal" κ:λ FLC ratio	0.26 – 1.65	0.50 – 2.00	0.70 – 2.25

Figure adapted from Witteles 2021[1]

A κ:λ FLC ratio skewed in one direction implies clonal production of κ or λ light chains (whichever is higher). In the setting of CKD, excess κ production by the bone marrow leads to a higher κ:λ FLC ratio.

*Normal κ:λ FLC ratios in the context of GFR (ml/min/1.73 m^2) per ACC 2023: If is GFR >60, 0.26-1.65; if GFR is 45 to 59, 0.46-2.62; if GFR is 30 to 44, 0.48-3.38; if GFR is <30, 0.54-3.30[2]

ACC, American College of Cardiology; AL, light chain; CKD, chronic kidney disease; FLC, free light chain; GFR, glomerular filtration rate; IgG, immunoglobulin G; SPIE, serum protein electrophoresis with immunofixation; UPIE, urine protein electrophoresis with immunofixation.

1. Witteles, Liedtke. *Circ Heart Fail*. 2021;14(4):e008225; 2. Kittleson et al. *J Am Coll Cardiol*. 2023;81(11):1076-1126.

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Ruling out AL by looking for clonal plasma cells: A 2-step process[1]

Step 1: Assess for clonality by measuring plasma cell byproducts

To measure **clonal antibody** (e.g., IgG-λ), use **serum** protein el…phoresis with immunofixation

Preferred test because … higher concentration …

To measure **clonal light chain** (e.g., λ light chain), use **urine** protein electrophoresis with immunofixation

…centrated in the urine; …nal light chains

Monoclonal protein assessment should include SPIE, UPIE, and serum FLC ratio testing.

Best practice:
If <u>any</u> of the three tests are abnormal, hematology referral and cardiac biopsy should be considered.

Step 2: …nction*

G…	
"N…	

…gure adapted from Witteles 2021[1]

A κ:λ FLC ratio skewed in one direction implies clonal production of κ or λ light chains (whichever is higher). In the setting of CKD, excess κ production by the bone marrow leads to a higher κ:λ FLC ratio.

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1. Witteles, Liedtke. *Circ Heart Fail*. 2021;14(4):e008225; 2. Kittleson et al. *J Am Coll Cardiol.* 2023;81(11):1076-1126.

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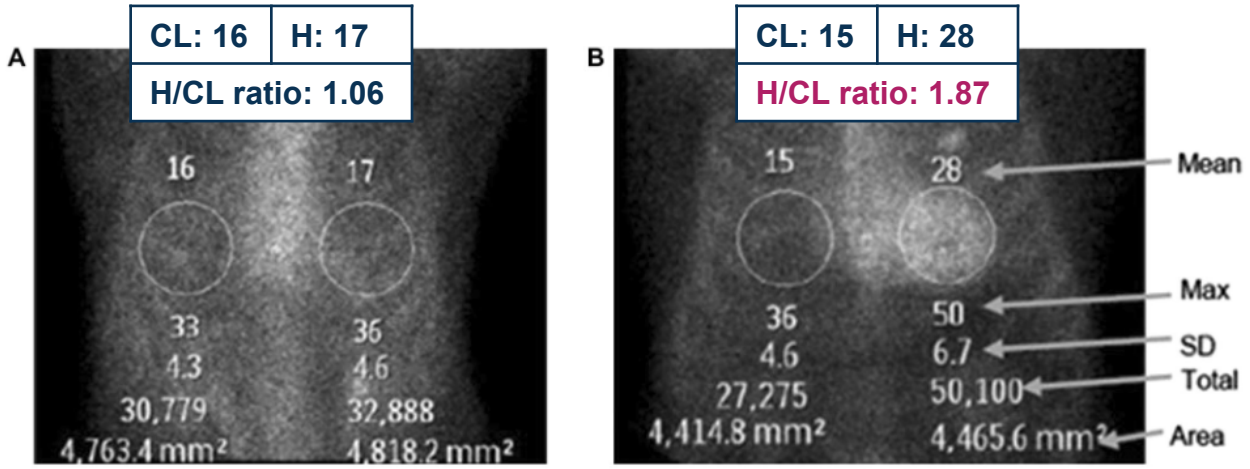
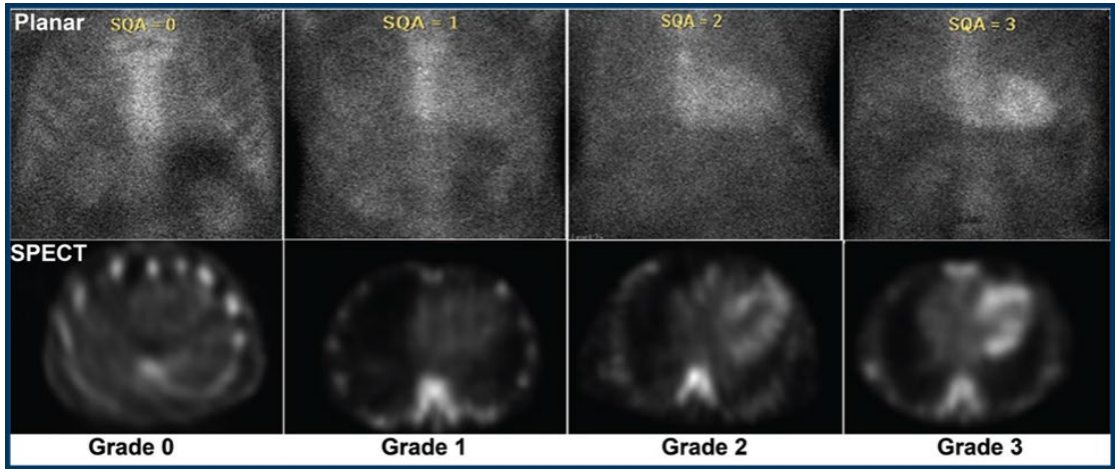
Nuclear scintigraphy imaging is a non-invasive method to reveal amyloid deposition in the heart[1-4]

Heart to contralateral lung (H/CL) ratio at 1 hour	ATTR amyloidosis
<1	Not suggestive
1-1.5	Equivocal
>1.5	Strongly suggestive

Grade	Myocardial PYP uptake	ATTR amyloidosis
Grade 0	No uptake, normal rib uptake	Not suggestive
Grade 1	Uptake less than rib uptake	Equivocal
Grade 2	Uptake equal to rib uptake	Strongly suggestive
Grade 3	Uptake greater than rib uptake with mild/absent rib uptake	



Images from Bokhari et al. 2018[1]



Images from Maurer et al. 2019[3]

^{99m}Tc-PYP, technetium-^{99m}-pyrophosphate; ATTR, transthyretin-mediated; SD, standard deviation; SPECT, single-photon emission computed tomography; SQA, semiquantitative analysis.

1. Bokhari et al. *J Nucl Cardiol*. 2018;25(1):181-190; 2. Dorbala et al. [published correction appears in *J Nucl Cardiol*. 2021;28(4):1761-1762]. *J Nucl Cardiol*. 2019;26(6):2065-2123; 3. Maurer et al. *Circ Heart Fail*. 2019;12(9):e006075; 4. Kittleson et al. *Circulation*. 2020;142(1):e7-e22.

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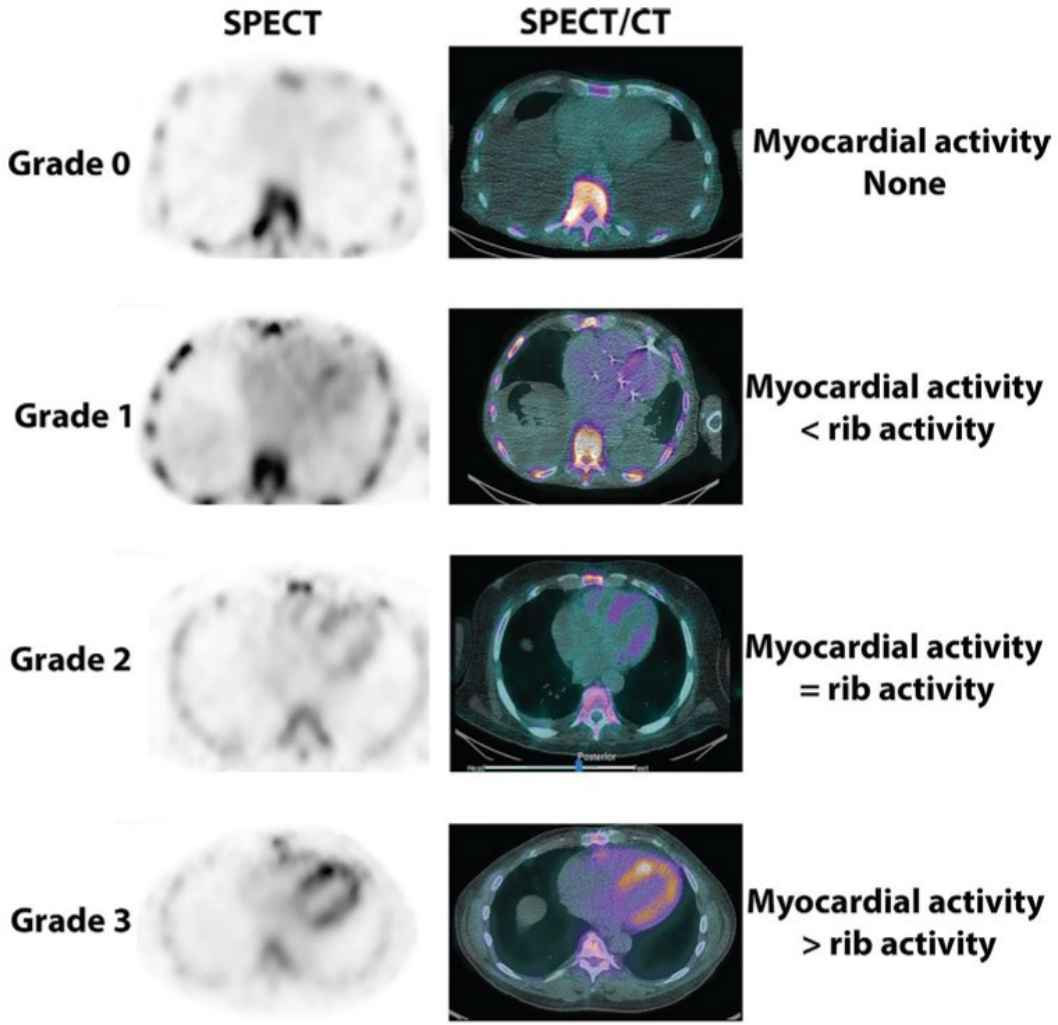
Nuclear scintigraphy imaging: Best practices

- **Planar imaging** should not be used alone for the diagnosis of ATTR amyloidosis[1]
- Timing of imaging: 1- vs. 3-hour[1]
  - If H/CL ratio at 1-hour is ≥1.5, considered positive
  - If H/CL ratio at 3-hours is ≥1.3, considered positive
  - Risk of false positive scan due to blood pooling
- Use **SPECT** to avoid false positives due to blood pooling on planar imaging[1]
- **SPECT/CT** is more powerful vs. SPECT alone for differentiating myocardial uptake vs. blood pool[2]
- If imaging is equivocal but clinical suspicion is high, **endomyocardial biopsy** recommended[1]



Images from Khor et al. 2023[3]

ATTR, transthyretin-mediated; H/CL, heart to contralateral lung; SPECT, single-photon emission computed tomography; SPECT/CT, single-photon emission computed tomography with computed tomography.

1. Dorbala et al. [published correction appears in *J Nucl Cardiol*. 2021;28(4):1761-1762]. *J Nucl Cardiol*. 2019;26(6):2065-2123; 2. Nichols et al. *Medicine (Baltimore)*. 2023;102(20):e33817; 3. Khor et al. *Radiology*. 2023;306(2):e221082.

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Genetic testing can be used to screen for and confirm hATTR amyloidosis

Genetic testing pearls

- *Ensure gene panel includes TTR*
- *Avoid overly broad screening*

- *Indicated for only P/LP variants*
- *Most useful for at-risk siblings vs. offspring*
- *Engage a genetic counselor if possible*

- *Ongoing assessment is required after P/LP variant identified*
- *Start clinical assessment 10 years prior to age of onset in proband patient (if applicable)*

Genetic testing process

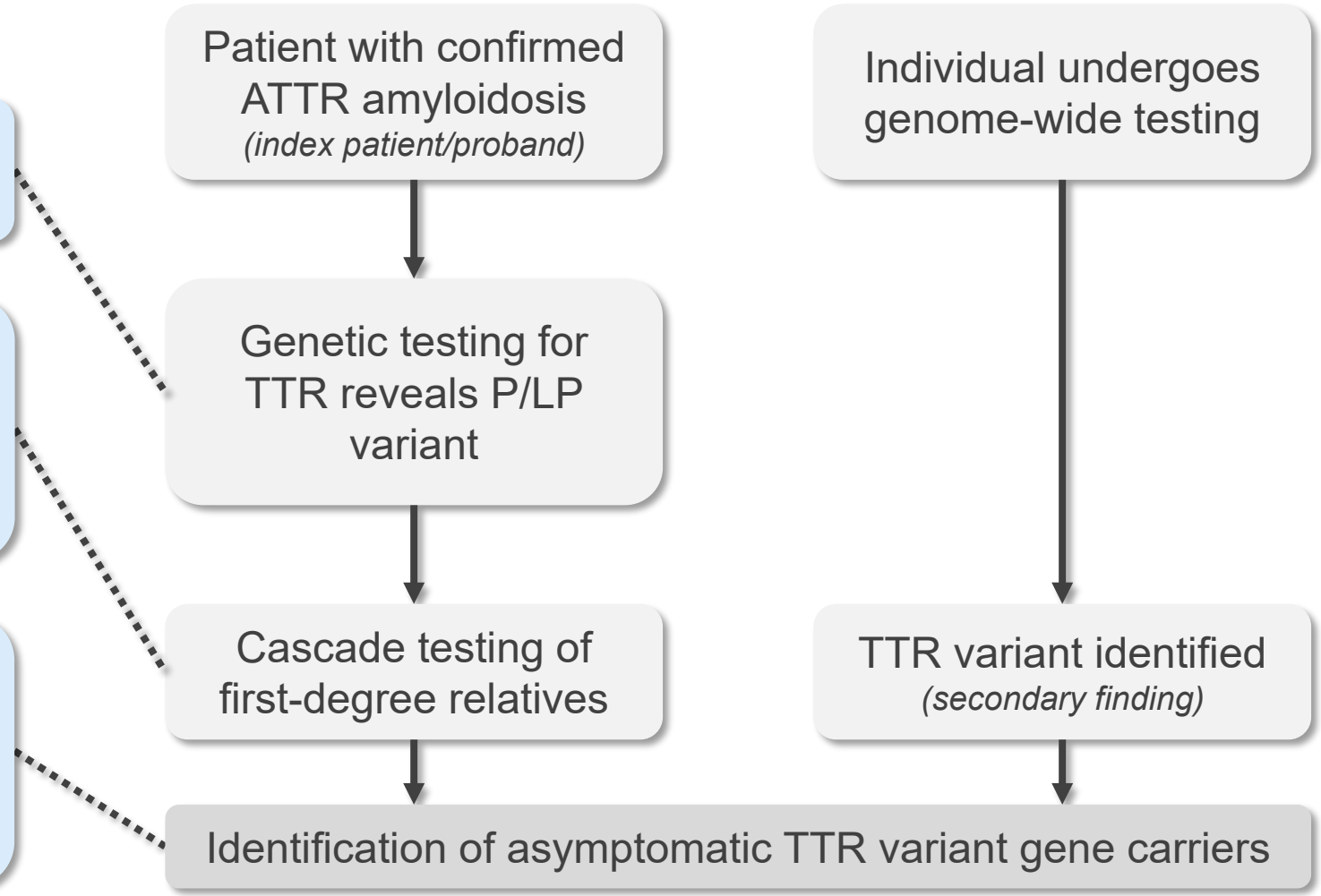

Figure adapted from Kittleson et al. 2023

hATTR, hereditary transthyretin-mediated; P/LP, pathogenic/likely pathogenic; TTR, transthyretin.

Kittleson et al. *J Am Coll Cardiol.* 2023;81(11):1076-1126.

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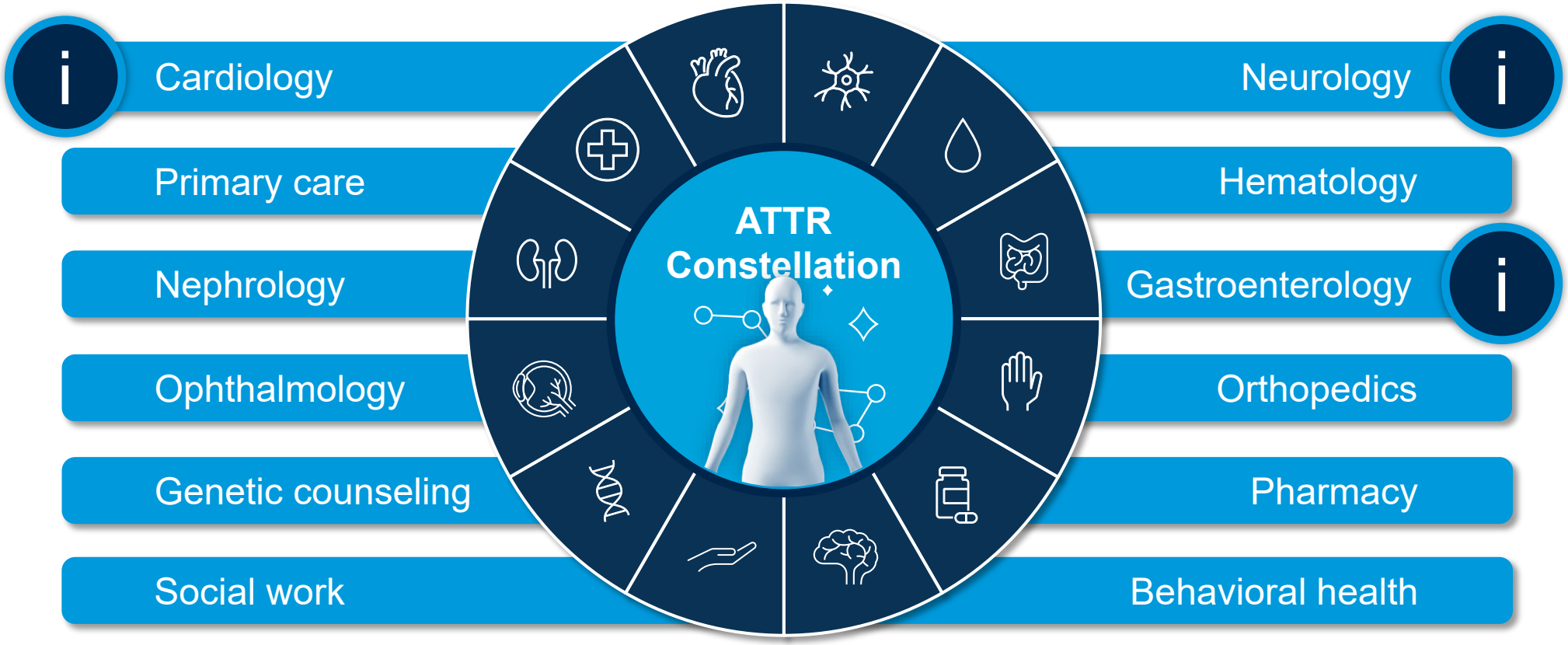
Management and Monitoring

The multisystemic nature of ATTR amyloidosis requires a multidisciplinary approach for the management of patients[1-3]



ATTR, transthyretin-mediated.

1. Nativi-Nicolau et al. *Heart Fail Rev*. 2022;27(3):785–93; 2. Karam et al. *XVIII Meeting of the International Society of Amyloidosis* 2022; Poster P192; 3. Obici et al. *BMJ Open*. 2023;13(9):e073130.

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Symptom management of cardiac manifestations

2023 ACC Expert Consensus Recommendations	
Symptom	**Therapy**
Heart failure	ARNI / ACE inhibitor / ARB, BB may worsen restrictive physiology MRA and SGLT2 inhibitor may be considered Loop + thiazide diuretic agents Heart transplant in select advanced patients
Arrhythmias	Atrial fibrillation: rate / rhythm + anticoagulation PPM for heart block ICD for VT / aborted SCD CRT if PPM-dependent?

ACC, American College of Cardiology; ARNI/ACE inhibitor/ARB, renin-angiotensin system inhibitors; BB, beta blocker; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; MRA, mineralocorticoid receptor antagonist; PPM, permanent pacemaker; SCD, sudden cardiac death; SGLT2, sodium glucose cotransporter 2; VT, ventricular tachycardia.

Kittleson et al. *J Am Coll Cardiol.* 2023;81(11):1076-1126.

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Symptom management of neurologic manifestations

2023 ACC Expert Consensus Recommendations	
Symptom	**Therapy**
Sensory neuropathy	**Pregabalin** **Gabapentin** **Tricyclic antidepressants** (amitriptyline, nortriptyline) **Selective serotonin-noradrenaline reuptake inhibitors** (duloxetine)
Orthostatic hypotension	**Non-pharmacologic**: • Compression stockings • Abdominal binder • Increased salt/fluid intake **Pharmacologic**: • Sympathomimetic agents (midodrine, droxidopa, pyridostigmine) • Agents to increase blood volume (salt tablets, fludrocortisone)

ACC, American College of Cardiology.
Kittleson et al. *J Am Coll Cardiol.* 2023;81(11):1076-1126.

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Symptom management of gastrointestinal manifestations

2023 ACC Expert Consensus Recommendations	
Symptom	**Therapy**
Nausea and early satiety	**Antiemetics** (ondansetron, promethazine) **Prokinetics** (metoclopramide, prucalopride)
Diarrhea	**Opioid-receptor antagonists** (loperamide, diphenoxylate/atropine, tincture of opium) **Bile salt binding** agents (cholestyramine, colesevelam, colestipol) **Somatostatin analog** (octreotide)
Constipation	**Laxatives** • Osmotic (polyethylene glycol) • Saline (magnesium citrate, magnesium sulfate) • Stimulant (senna) **Secretory agents** (linaclotide)

ACC, American College of Cardiology.
Kittleson et al. *J Am Coll Cardiol.* 2023;81(11):1076-1126.

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Current approved and investigational therapeutic approaches for ATTR amyloidosis

Suppression of TTR synthesis:

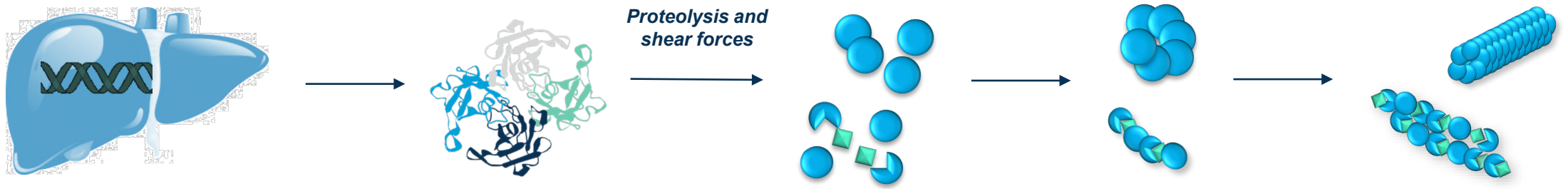
Liver transplantation
Gene silencing (siRNA, ASO)
Gene editing (CRISPR-Cas9)

Stabilization of TTR tetramer:

TTR stabilizer

Amyloid fibril degradation/ reabsorption:

Monoclonal antibody targeting misfolded TTR



***TTR* gene expressed in liver** | **TTR tetramer** | **TTR monomers** | **Truncated and misfolded TTR** | **Amyloid fibrils**

Image adapted from Ando et al. 2022

ASO, antisense oligonucleotide; ATTR, transthyretin-mediated; CRISPR, clustered regularly interspaced short palindromic repeats; siRNA, small interfering ribonucleic acid; TTR, transthyretin.
Ando et al. *Amyloid.* 2022; 29(3):143–55.

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Routine follow-up to monitor disease progression is critical for patients with hATTR amyloidosis

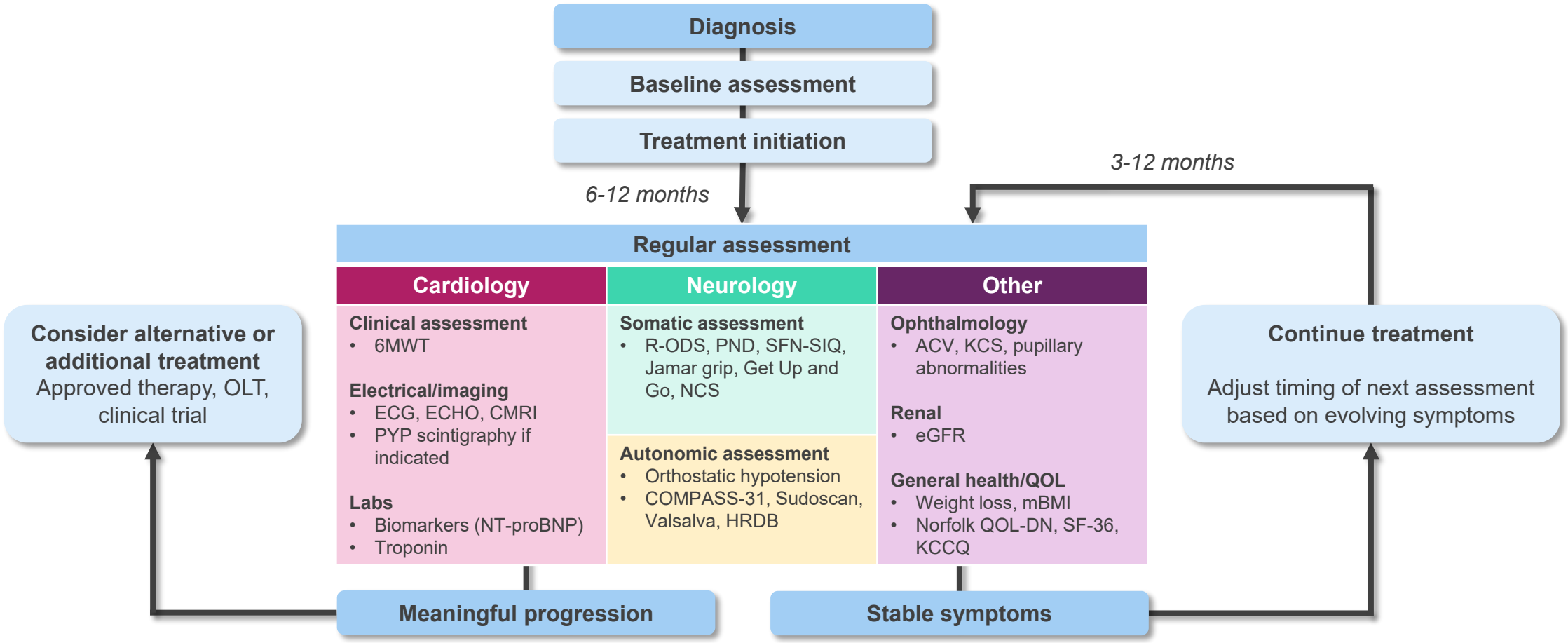

Figure adapted from Adams et al. 2021

6MWT, 6-minute walk test; ACV, abnormal conjunctival vessel; CMRI, cardiac magnetic resonance imaging; COMPASS-31, Composite Autonomic Symptom Score 31; ECG, electrocardiogram; ECHO, echocardiogram; eGFR, estimated glomerular filtration rate; hATTR, hereditary transthyretin-mediated; HRDB, heart rate deep breathing; KCCQ, Kansas City Cardiac Questionnaire; KCS, keratoconjunctivitis sicca; mBMI, modified body mass index; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; NCS, nerve conduction study; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; OLT, orthotropic liver transplantation; PND, polyneuropathy disability; PYP, pyrophosphate; QOL, quality of life; R-ODS, Rasch built Overall Disability Scale; SF-36, 36 item Short Form Health Survey; SFN-SIQ, small fiber neuropathy and symptom inventory questionnaire.

Adams et al. *Orphanet J Rare Dis*. 2021;16(1):411.

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Patient case*

- **HPI**:
  - MP, a 70-year-old African American male, presents to your cardiology clinic for follow up after being diagnosed with heart failure.
  - MP complains of shortness of breath, fatigue, weakness in hands, and loss of sensation in feet.
  - **MP diagnosed with V122I hATTR amyloidosis.**
- **PMH**:
  - Hypertension
  - Peripheral neuropathy
  - Bilateral carpal tunnel syndrome
- **Family history**:
  - CHF, type 2 diabetes (father)
- **Surgical history**:
  - Bilateral carpal tunnel release (2018)
- **Current medications**:
  - Lisinopril 5 mg PO QD
  - Furosemide 20 mg PO BID
  - Gabapentin 300 mg PO TID
- **Previous medications**:
  - Metoprolol
    - Discontinued due to hypotension, fatigue, and bradycardia
- **Labs**:
  - eGFR: 60 mL/min/1.73m^2
  - NT-proBNP: 2145 pg/mL
  - Troponin T: 0.04 ng/mL
- **Imaging**:
  - Echocardiogram
    - EF: 45%
    - LV wall thickness: 1.8 cm
    - Relative wall thickness: 0.8

What pharmacologic and/or non-pharmacologic therapies would you consider?

What labs would you perform routinely?

How will you monitor disease progression/ improvement?

What steps would you recommend for MP's family?

Which specialties should MP follow up with?

*This patient profile was created via a review of published literature and is not an actual patient.

BID, two times daily; CHF, congestive heart failure; EF, ejection fraction; eGFR, estimated glomerular filtration rate; hATTR; hereditary transthyretin-mediated; HPI, history of present illness; LV, left ventricular; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PMH, past medical history; PO, by mouth; QD, once daily; TID, three times daily.

Main Takeaways

- V122I is the most common *TTR* variant in the United States and is most prevalent in patients of African descent[1,2]
- V122I variant carriers have significantly higher heart failure incidence and heart failure mortality compared to non-carriers[3]
- V122I hATTR amyloidosis is associated with greater disease burden and worse prognosis compared to other *TTR* variants and wtATTR amyloidosis[4]
- Awareness of extracardiac ATTR amyloidosis symptoms is critical, as these often predate cardiac manifestations[5-7]
- Diagnosis can be made by following the ACC algorithm, noting the need to rule out AL, the importance of genetic testing to confirm variant status, and the value of genetic counseling[1]
- For the best possible clinical outcomes, timely diagnosis and treatment are critical[1]

ACC, American College of Cardiology; AL, light chain; ATTR, transthyretin-mediated; hATTR, hereditary transthyretin-mediated; TTR, transthyretin; wtATTR, wild-type transthyretin-mediated.

1. Kittleson et al. *J Am Coll Cardiol.* 2023;81(11):1076-1126; 2. Buxbaum, Ruberg. *Genet Med*. 2017;19(7):733-742; 3. Parcha et al. *JAMA*. 2022;327(14):1368-1378; 4. Goyal et al. *Heart Fail Rev*. 2021;27(3):849-856; 5. Zampino et al. *Neurology*. 2023;100(19):e2036-e2044; 6. Kaku et al. *Amyloid*. 2022;29(3):184-189; 7. Grogan et al. Poster presented at: Heart Failure Society of America (HFSA), September 13-16, 2019; Philadelphia, PA.

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Amyloidosis and Rare Disease Advocacy Groups

Amyloidosis Foundation

Amyloidosis Research Consortium

Amyloidosis Support Groups

International Society of Amyloidosis

National Organization for Rare Disorders

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