AAVBC
AMERICAN ACADEMY OF VALUE BASED CARE

Amyloidosis

Quick Reference Guide

2026

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1 CLINICAL SNAPSHOT

Definition: Amyloidosis is a group of diseases defined by extracellular deposition of **misfolded proteins** (**amyloid fibrils**) in tissues and organs. **Four systemic subtypes** shape primary care decision-making: **AL** (immunoglobulin light chain, plasma cell–driven), **ATTRwt** (age-related wild-type transthyretin, predominantly cardiac), **ATTRv** (hereditary transthyretin variant, cardiac and/or polyneuropathic), and **AA** (secondary to chronic inflammatory disease). Clinical impact and treatment depend entirely on subtype: AL requires prompt hematology/oncology evaluation for plasma-cell–directed therapy; ATTR requires TTR-targeted disease-modifying therapy**;** AA is managed by treating the underlying inflammatory condition. No curative therapy currently exists for systemic amyloidosis; treatment aims to halt amyloid production, manage symptoms, and preserve organ function.[1–4]

ICD-10 Codes (effective October 2025):[5] **E85.81** (light chain (AL) amyloidosis), **E85.82** (wild-type transthyretin-related amyloidosis, ATTRwt), **E85.1** (neuropathic heredofamilial amyloidosis= ATTRv with neuropathy), **E85.4** (organ-limited amyloidosis), **E85.3** (secondary systemic amyloidosis (AA) = requires coding the underlying inflammatory condition separately), **E85.9** (amyloidosis, unspecified: reserve **ONLY** when subtype cannot be confirmed after full workup). In cardiac amyloidosis, **E85.4** must be sequenced **BEFORE I43** (cardiomyopathy in diseases classified elsewhere).[2]

Prevalence and Diagnostic Delay: Systemic amyloidosis is **systematically underdiagnosed**. AL amyloidosis has an estimated US incidence of **12 to 17 cases per million person-years**, with approximately 3,800 to 4,000 new cases diagnosed annually and a rising prevalence now estimated at **40 to 69 per million adults**.[6–8] Twenty-five percent of AL amyloidosis patients **die within 6 months of diagnosis**, driven largely by advanced cardiac damage at presentation; early-stage patients achieve approximately 80% five-year survival with contemporary treatment compared with less than 30% for advanced-stage disease.[9,10] The median diagnostic delay in AL amyloidosis is **2.7 years** from symptom onset, with 50% of patients seeing **five or more physician types before diagnosis**.[11] Other amyloidosis subtypes are less frequently diagnosed but may be more prevalent. Autopsy studies demonstrate ATTR amyloid deposits in 20 to 25% of adults older than 80 years, with wild-type ATTR-CM estimated at **155 to 191 cases** per million persons.[9–11] **ATTRv** (hereditary ATTR) due to the Val122Ile (V122I) variant, the most common pathogenic TTR variant in the US, is carried by approximately **3.4% of African Americans** (approximately 1.5 million individuals) and is associated with development of ATTR cardiomyopathy **after age 60**, with penetrance estimates ranging from 7% to 39% depending on diagnostic modality.[2,12]

AAVBC PERSPECTIVE

*From a value-based care perspective, early recognition and accurate clinical coding of systemic amyloidosis are essential for improving care coordination, reducing avoidable hospital utilization, and preserving patient function and quality of life. Use of specific ICD-10-CM **E85.X** subtype codes, **rather than unspecified E85.9 coding**, can support more precise diagnosis tracking, specialist referral pathways, reimbursement alignment, and closed loop care delivery across multidisciplinary teams. Earlier recognition and diagnosis also help connect patients to appropriate treatment strategies focused on **symptom management**, **organ preservation**, and optimization or adjustment of therapies used to manage coexisting comorbidities that may be **impacted by amyloid disease progression**. Treatment intensity, care planning, and*

goals-of-care discussions should prioritize frailty and biological age rather than chronological age to support individualized and clinically appropriate management decisions.

Systemic Amyloidosis ICD-10-CM Codes that Map to HCC 50

AMYLOIDOSIS ICD-10[12]	DIAGNOSTIC CRITERIA	CODING NOTES[1,3,4,8,10]
E85.0 Non-neuropathic heredofamilial amyloidosis	**Pathogenic TTR variant** (e.g., V122I, T60A) + documented cardiomyopathy or organ involvement **WITHOUT** polyneuropathy	Sequence: E85.0 → I43 → I50.3x if HFpEF; TTR gene sequencing required; cascade genetic testing for first-degree relatives
E85.1 Neuropathic heredofamilial amyloidosis	**Pathogenic TTR variant** (e.g., V30M, T60A) + **documented polyneuropathy** (EMG/NCS or skin biopsy confirmed)	Sequence: E85.1 → G63 (neuropathy manifestation) ± I43 if concurrent cardiomyopathy; do NOT assign for asymptomatic carriers
E85.2 Heredofamilial amyloidosis, unspecified	**Pathogenic TTR variant confirmed**; phenotype not yet characterized (awaiting cardiac/neuro workup)	Placeholder only (but does map to HCC 50); **reclassify to E85.0 or E85.1** once organ involvement documented; avoid long-term use
E85.3 Secondary systemic (AA) amyloidosis	Tissue biopsy with AA protein typing (Congo red + MS) + concurrent chronic inflammatory disease	**Co-code** underlying disease (e.g., M05.xx RA, K50.xx Crohn, M45.x AS); E85.3 alone is **clinically incomplete**
E85.4 Organ limited amyloidosis	Tissue-confirmed amyloid in single organ + systemic workup negative	Use only after **systemic disease excluded**; sequence E85.4 before manifestation code (e.g., E85.4 → I43 for cardiac-limited)
E85.81 Light chain (AL amyloidosis)	Congo red + tissue biopsy with LC typing by mass spectrometry + plasma cell dyscrasia (FLC + SIFE + UIFE)	Document all organ involvement codes alongside; NCCN: amyloid subtyping by MS is required;[4] bone marrow biopsy + fat pad sampling standard
E85.82 Wild-type ATTR (ATTRwt) amyloidosis	Perugini grade 2-3 PYP uptake + negative monoclonal protein screen (FLC + SIFE + UIFE); OR tissue biopsy with TTR typing showing wild-type	**PYP alone insufficient** (can be positive in AL); sequence E85.82 → I43 → I50.3x; TTR gene sequencing confirms wild-type vs. variant
E85.89 Other amyloidosis	Tissue-confirmed amyloidosis with **precursor protein not fitting:** AL, ATTR, or AA categories (e.g., AFib, AApoAI, ALys)	Specify precursor protein in documentation; rare subtypes require MS-based typing at reference lab

AMYLOIDOSIS ICD-10[12]	DIAGNOSTIC CRITERIA	CODING NOTES[1,3,4,8,10]
E85.9 Amyloidosis, unspecified	**AVOID**: acceptable only when tissue typing is incomplete or inconclusive after full workup	**Most common coding error**: using E85.9 when subtype is known; AL requires chemotherapy, ATTR requires stabilizers/ silencers; wrong code may signal wrong care pathway

ABBREVIATIONS: TTR = transthyretin; HFpEF = heart failure with preserved ejection fraction; I43 = cardiomyopathy in diseases classified elsewhere; I50.3x = heart failure with preserved ejection fraction codes; EMG = electromyography; NCS = nerve conduction studies; G63 = polyneuropathy in diseases classified elsewhere; HCC = Hierarchical Condition Category; AA = serum amyloid A protein; MS = mass spectrometry; RA = rheumatoid arthritis; AS = ankylosing spondylitis; AL = immunoglobulin light chain amyloidosis; LC = light chain; FLC = free light chain; SIFE = serum immunofixation electrophoresis; UIFE = urine immunofixation electrophoresis; NCCN = National Comprehensive Cancer Network; ATTRwt = wild-type transthyretin amyloidosis; PYP = technetium-99m pyrophosphate scintigraphy; AFib = fibrinogen amyloidosis; AApoAI = apolipoprotein A-I amyloidosis; ALys = lysozyme amyloidosis

Risk-Adjusted Care Resources per Patient/Year[15,16]

Risk-adjusted care resource allocation — MA base rate ($10,402) × RAF coefficient for HCC 50: 0.648

Systemic Amyloidosis

~$6,740

HCC 50 · RAF 0.648

RAF values represent the Community Non-Dual Eligible Aged (CNA) coefficient from the 2026 CMS-HCC model; values vary across patient populations based on eligibility and care setting

2 RECOGNITION AND DIAGNOSIS

Screenings for Suspected Amyloidosis Covered Under Medicare Part B

TEST[2–4,13]	FREQUENCY	CPT CODE	CLINICAL INDICATION[2–4,13]
Serum free light chain (FLC) assay	At suspicion; serial for monitoring	83520	First-line AL screening = part of three-test panel (**FLC** + SIFE + UIFE) with combined sensitivity 99% for AL; kappa/lambda ratio can be **falsely normal** in renal impairment: evaluate absolute values along with ratio

TEST[2–4,13]	FREQUENCY	CPT CODE	CLINICAL INDICATION[2–4,13]
Serum immunofixation electrophoresis (SIFE)	At suspicion; with FLC + UIFE panel	86334	**Preferred over SPEP alone** (IFE >90% vs. SPEP ~70% sensitivity for monoclonal protein); required before relying on PYP alone for ATTR diagnosis
Urine immunofixation electrophoresis (UIFE)	At suspicion; with FLC + SIFE panel	86335	Completes AL screening panel; must use 24-h urine collection with concurrent UPEP; abnormal light-chain excretion may be earliest laboratory signal
Technetium-99m PYP cardiac scintigraphy	Once at suspicion (repeat only if clinically indicated)	78451 (planar); 78452 (SPECT)	Indicated in HFpEF with **unexplained LV wall thickness ≥14 mm**, low-voltage ECG, or ATTR-CM clinical clues; grade 2-3 uptake has 100% PPV for ATTR-CM ONLY when concurrent monoclonal screen (FLC + SIFE + UIFE) is negative; SPECT required to confirm myocardial vs. blood pool uptake
Transthoracic echocardiography with GLS	At initial workup; serial for monitoring	93306 (complete); 93320 (Doppler)	**Apical sparing strain pattern** characteristic of amyloid cardiomyopathy; low QRS voltage despite wall thickening is a high-yield ECG-echo discordance signal; LV wall thickness ≥12 mm with diastolic dysfunction raises suspicion
NT-proBNP and troponin T/I	At diagnosis; serial for staging and monitoring	83880 (NT-proBNP); 84484 (troponin)	Required for Mayo 2012 **AL staging** (NT-proBNP ≥332 ng/L);[14] NT-proBNP ≥1800 ng/L, TnT ≥0.025 µg/L, dFLC ≥18 mg/dL for 2012) and Mayo/NAC ATTR-CM staging (NT-proBNP ≥3000 ng/L, TnT ≥0.05 ng/mL)[15]
TTR gene sequencing	Once after ATTR-CM diagnosis confirmed	81404 (molecular pathology, Level 5)	Required to distinguish ATTRwt from ATTRv;[16] determines eligibility for **TTR silencer therapies** and triggers cascade genetic testing of first-degree relatives
Cardiac MRI (CMR)	At initial workup if feasible	75561 (cardiac MRI with contrast)	Tissue characterization (ECV, LGE) aids differentiation from HCM, sarcoidosis, Fabry; cannot distinguish AL from ATTR alone; **not required if PYP diagnostic**
Amyloid tissue subtyping by mass spectrometry	Once at tissue confirmation	88374 (morphometric analysis, quantitative) or institutional-specific	MS-based subtyping required for all Congo red-positive tissue specimens;[4] LC-MS/MS has 88% sensitivity and 96% specificity for precursor protein identification;[17] g**old standard for distinguishing** AL, ATTR, AA, and rare subtypes

TEST[2–4,13]	FREQUENCY	CPT CODE	CLINICAL INDICATION[2–4,13]

ABBREVIATIONS: FLC = free light chain; AL = light chain amyloidosis; SIFE = serum immunofixation electrophoresis; UIFE = urine immunofixation electrophoresis; SPEP = serum protein electrophoresis; IFE = immunofixation electrophoresis; PYP = technetium-99m pyrophosphate; ATTR = transthyretin amyloidosis; UPEP = urine protein electrophoresis; HFpEF = heart failure with preserved ejection fraction; LV = left ventricular; ECG = electrocardiogram; ATTR-CM = transthyretin amyloid cardiomyopathy; PPV = positive predictive value; SPECT = single-photon emission computed tomography; GLS = global longitudinal strain; QRS = QRS complex (ventricular depolarization); NT-proBNP = N-terminal pro-B-type natriuretic peptide; TnT = troponin T; dFLC = difference between involved and uninvolved free light chains; NAC = UK National Amyloidosis Centre; TTR = transthyretin; ATTRwt = wild-type transthyretin amyloidosis; ATTRv = hereditary/variant transthyretin amyloidosis; CMR = cardiac magnetic resonance imaging; ECV = extracellular volume fraction; LGE = late gadolinium enhancement; HCM = hypertrophic cardiomyopathy; MS = mass spectrometry; LC-MS/MS = liquid chromatography-tandem mass spectrometry; AA = secondary systemic amyloidosis (serum amyloid A protein); CPT = current procedural terminology

Subtle Early Signs in Older Adults

SIGN/SYMPTOM[2–4,16]	CLINICAL SIGNIFICANCE[2–4,16]
Bilateral carpal tunnel syndrome (CTS), especially in men >60 yrs	Precedes ATTR cardiac diagnosis by 5–10 years; document **BILATERALITY explicitly**; this is the single highest-yield musculoskeletal red flag; do not dismiss as 'occupational' in an older adult
HFpEF with left ventricular wall thickness ≥14 mm	ATTR-CM present in **6–17% of HFpEF patients** >60 y; apply the ATTR-CM clinical score: a score ≥6 warrants PYP scintigraphy (sensitivity 93%, specificity 62%)
Lumbar spinal stenosis (amyloid deposits in ligamentum flavum)	TTR deposits are present in the **ligamentum flavum** in up to one-third of older surgical patients; frequently missed and undercoded; document when present and consider cardiac evaluation
Spontaneous biceps tendon rupture	Precedes ATTR cardiac diagnosis by ~5 years (median). Pathognomonic red flag; evaluate for ATTR-CM
Orthostatic hypotension, gastroparesis, erectile dysfunction, chronic diarrhea	Autonomic neuropathy is a multisystem amyloidosis signal; complicates antihypertensive and diuretic management: a false reassurance of 'good blood pressure control' may be masking autonomic disease
Macroglossia or periorbital purpura	Pathognomonic but low-sensitivity (macroglossia ~15%) signs of **AL amyloidosis**; presence highly specific; absence does not exclude; wWhen seen, initiate FLC + SIFE + UIFE immediately[4]

ABBREVIATIONS: AL = light chain amyloidosis; ATTR = transthyretin amyloidosis; ATTR-CM = transthyretin amyloid cardiomyopathy; CTS = carpal tunnel syndrome; FLC = free light chain; HFpEF = heart failure with preserved ejection fraction; PYP = technetium-99m pyrophosphate; SIFE = serum immunofixation electrophoresis; TTR = transthyretin; UIFE = urine immunofixation electrophoresis

Risk Factors

FACTOR[2–4,16]	RISK SIGNAL[2–4,16]	NOTES[2–4,16]
Age ≥60 years with HFpEF and increased LV wall thickness	ATTRwt present in **6–17%** of this population; rises from ~5% in the sixth decade to ~20% in the ninth decade	Apply the ATTR-CM clinical score (Davies 2022);[18] **score ≥6** warrants PYP scintigraphy with concurrent monoclonal screen
Male sex (ATTRwt specialty-center cohorts: 81–98% male; community cohorts closer to 50%)	Sex bias in referral patterns means women with ATTRwt are systematically **under-recognized**	Evaluate women with the s**ame index of suspicion** as men when red flags are present; do not require male sex to trigger workup
African American race (V122I TTR variant)	~1.5 million carriers in the U.S: (3.4–3.5% of African Americans);[13] 10% penetrance at age 65, rising to 39% by the eighth decade	Increased heart failure risk and mortality at age >60; consider genetic testing after ATTR diagnosis[13]
Ancestral origin with established hereditary TTR variants (Portuguese/ Swedish V30M; Irish T60A; others)	Penetrance varies dramatically by ancestry; V30M: 80% in Portugal vs. 11% in Sweden	Ancestral origin critically shapes clinical risk and genetic counseling; family history of neuropathy or early-onset cardiomyopathy is highly informative
MGUS (monoclonal gammopathy of undetermined significance) or multiple myeloma	Relative risk of AL amyloidosis 8.8; 1% incidence in MGUS cohort of 1,384 patients; **10–15% of myeloma patients develop AL** (38% have Congo red–positive fat/ marrow deposits)	**Annual monoclonal screen in MGUS**; proactive AL screening in myeloma patients with organ dysfunction

ABBREVIATIONS: AL = light chain amyloidosis; ATTR = transthyretin amyloidosis; ATTRwt = wild-type transthyretin amyloidosis; FLC = free light chain; HFpEF = heart failure with preserved ejection fraction; LV = left ventricular; MGUS = monoclonal gammopathy of undetermined significance; PYP = technetium-99m pyrophosphate; RA = rheumatoid arthritis; SIFE = serum immunofixation electrophoresis; T60A = Thr60Ala TTR variant; TTR = transthyretin; UIFE = urine immunofixation electrophoresis; V30M = Val30Met TTR variant; V122I = Val122Ile TTR variant

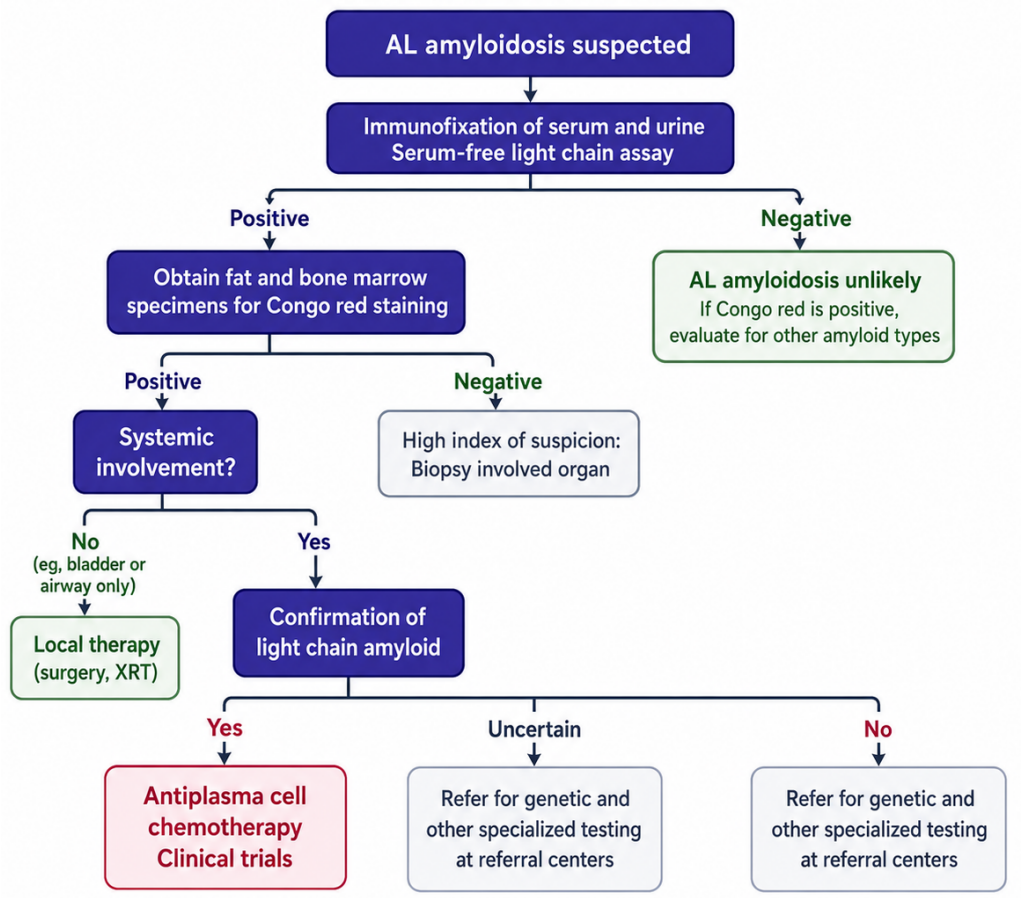
Diagnostic Thresholds

TEST/ MARKER[2–4,16]	DIAGNOSIS CRITERION[2–4,16]	NOTES[2–4,16]
Three-test monoclonal screen (FLC + SIFE + UIFE)	Combined sensitivity **99% for AL**; negative panel required before relying on PYP alone for ATTR diagnosis	Kappa/lambda ratio can be falsely normal in reduced kidney function: evaluate absolute free light-chain values; a normal ratio alone does not exclude AL[4]

TEST/ MARKER[2–4,16]	DIAGNOSIS CRITERION[2–4,16]	NOTES[2–4,16]
Technetium-99 m PYP scintigraphy (Perugini grade)	Grade 0 = no uptake; 1 = cardiac < rib; 2 = cardiac = rib; 3 = cardiac > rib; Grade 2–3 has **100% PPV for ATTR-CM ONLY** with concurrent negative monoclonal screen	'PYP positive' alone does not diagnose ATTR-CM; PYP can be positive in AL: concurrent FLC + SIFE + UIFE is mandatory[3,4]
ATTR-CM clinical score (Davies 2022) in HFpEF[18]	**≥6 points** warrants PYP scintigraphy; sensitivity 93%, specificity 62%. Points: male sex (+1); age 60–69 (+1), 70–79 (+2), ≥80 (+3); no HTN history (+1); HTN documented (−1); bilateral CTS (+2); pacemaker/ICD (+1); LV wall thickness ≥14 mm (+2)	PCP-friendly screening tool; guides therapy escalation
Abdominal fat pad aspiration + Congo red (± bone marrow biopsy)	Fat pad alone positive in **70–75% of AL**; combined fat pad + BM identifies 85%; green birefringence under polarized light confirms amyloid	IHC alone insufficient for typing per NCCN 2026;[4] mass spectrometry is mandatory for definitive AL vs. ATTR vs. AA distinction
Echocardiogram with global longitudinal strain	Apical sparing strain pattern characteristic of amyloid cardiomyopathy; LV wall thickness ≥12 mm unexplained by **hypertension or aortic stenosis**	Early-stage ATTR-CM **may not** show increased wall thickness: low QRS voltage discordant with wall thickening and GLS abnormalities may **precede classic echocardiographic findings**[19]

ABBREVIATIONS: AL = light chain amyloidosis; ATTR = transthyretin amyloidosis; ATTR-CM = transthyretin amyloid cardiomyopathy; BM = bone marrow; CTS = carpal tunnel syndrome; dFLC = difference in involved and uninvolved free light chain; FLC = free light chain; GLS = global longitudinal strain; HFpEF = heart failure with preserved ejection fraction; HTN = hypertension; ICD = implantable cardioverter-defibrillator; IHC = immunohistochemistry; LV = left ventricular; NCCN = National Comprehensive Cancer Network; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PCP = primary care provider; PPV = positive predictive value; PYP = technetium-99m pyrophosphate; SIFE = serum immunofixation electrophoresis; UIFE = urine immunofixation electrophoresis

Simplified Diagnostic Pathway for Suspected AL Amyloidosis



Diagnostic pathway for suspected AL amyloidosis, beginning with monoclonal protein screening using serum and urine immunofixation plus serum free light chain testing. Positive screening prompts tissue confirmation with Congo red staining, assessment for systemic involvement, and amyloid typing to guide referral, organ-directed evaluation, and plasma cell–directed therapy when AL amyloidosis is confirmed.

CLINICAL PEARL — RAISE THE INDEX OF SUSPICION

Amyloidosis is systematically underdiagnosed with an average diagnostic delay 2–3 years, with patients seeing >5 specialists before the diagnosis is established.[20] Three common-seeming findings should **automatically prompt amyloidosis consideration** in a Medicare-age patient: (**1**) bilateral carpal tunnel syndrome in a man >60 y = precedes ATTR cardiac diagnosis by 5–10 years; (**2**) HFpEF with LV wall thickness ≥14 mm = **ATTR-CM is present in 6–17% of this population**; (**3**) nephrotic-range proteinuria (>3.5 g/day) without diabetes or long-standing hypertension = screen for AL with monoclonal screen. None of these clinical signs should be considered 'age-related' **until amyloidosis has been ruled out**.

Common Oversights

OVERSIGHT/SHORTCUT	WHY IT MATTERS — WHAT TO DO INSTEAD
Using E85.9 (unspecified) when subtype is known	**Single most common amyloidosis coding error**; AL needs chemotherapy whereas ATTR needs TTR stabilizers; Insufficient coding may signal wrong care pathway = use **E85.81** (AL), **E85.82** (ATTRwt), **E85.0 or E85.1** (ATTRv), or **E85.3** (AA) when confirmed
Treating a positive PYP scan as sufficient to diagnose ATTR-CM	PYP can be positive in AL amyloidosis;[4] without a concurrent negative monoclonal protein screen, **AL cannot be excluded**
Attributing bilateral CTS, HFpEF, or spinal stenosis to 'normal aging'	These are amyloidosis screening triggers in Medicare patients often misattributed as “age-related symptoms” ; reframe: red flag present → initiate three-test monoclonal screen + echocardiogram[3,4]

ABBREVIATIONS: AA = secondary systemic amyloidosis; AL = light chain amyloidosis; ATTR-CM = transthyretin amyloid cardiomyopathy; ATTRv = hereditary/variant transthyretin amyloidosis; ATTRwt = wild-type transthyretin amyloidosis; CTS = carpal tunnel syndrome; FLC = free light chain; GI = gastrointestinal; HFpEF = heart failure with preserved ejection fraction; I43 = cardiomyopathy in diseases classified elsewhere; I50.3x = HFpEF codes; PYP = technetium-99m pyrophosphate; SIFE = serum immunofixation electrophoresis; TTR = transthyretin; UIFE = urine immunofixation electrophoresis; V122I = Val122Ile TTR variant

Key Differentials in Elderly

PRESENTATION	DIFFERENTIAL[2–4,16]	KEY TESTS[2–4,16]
HFpEF with LV wall thickness ≥14 mm	ATTR-CM (**6–17%** in this population), AL cardiomyopathy, hypertensive cardiomyopathy, hypertrophic cardiomyopathy, Fabry disease, degenerative aortic stenosis (16% ATTR-CM co-prevalence)	Monoclonal screen; ATTR-CM score; PYP scintigraphy **if score ≥6**; echocardiogram with strain; NT-proBNP and troponin
Nephrotic-range proteinuria (>3.5 g/day) in elderly without long-standing diabetes or HTN	AL amyloidosis (**renal involvement ~70% of AL**), AA amyloidosis, diabetic nephropathy, membranous nephropathy, minimal change disease	Monoclonal screen; **24-hour urine protein + creatinine**; renal ultrasound; kidney biopsy with Congo red + mass spectrometry if screening positive[4]
Peripheral sensory polyneuropathy with autonomic features (orthostatic hypotension, gastroparesis, ED)	ATTRv amyloidosis, diabetic neuropathy, chemotherapy-induced neuropathy, paraproteinemia- associated neuropathy	Monoclonal screen; TTR gene sequencing if clinical suspicion high; [3,13] EMG/NCS; orthostatic vital signs; autonomic testing

PRESENTATION	DIFFERENTIAL[2–4,16]	KEY TESTS[2–4,16]
Bilateral CTS in a man >60 y with low-voltage ECG	ATTR-CM (**CTS precedes by 5–10 y**);[10] primary cardiac amyloidosis; acromegaly; hypothyroidism	**ATTR-CM score**;[3,10] echocardiogram with strain; PYP with concurrent monoclonal screen; NT-proBNP; troponin; document CTS BILATERALITY
Macroglossia, periorbital purpura, or jaw claudication	AL amyloidosis (low sensitivity ~15%, high specificity); hereditary angioedema (episodic); Sjögren syndrome-related	Monoclonal screen immediately; **fat pad aspiration** with Congo red; oncology/hematology consult if any positive

ABBREVIATIONS: AA = secondary systemic amyloidosis; AL = light chain amyloidosis; ATTR-CM = transthyretin amyloid cardiomyopathy; ATTRv = hereditary/variant transthyretin amyloidosis; CTS = carpal tunnel syndrome; ECG = electrocardiogram; ED = erectile dysfunction EMG = electromyography; FLC = free light chain; HFpEF = heart failure with preserved ejection fraction; HTN = hypertension; LV = left ventricular; NCS = nerve conduction study; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PYP = technetium-99m pyrophosphate; SIFE = serum immunofixation electrophoresis; TTR = transthyretin; UIFE = urine immunofixation electrophoresis

Comorbidity Screening

CONDITION	PREVALENCE/ ASSOCIATION[2–4,16]	SCREENING APPROACH[2–4,16]
HFpEF with LV wall thickness ≥14 mm	ATTR-CM present in **6–17%** of patients >60 y	Apply ATTR-CM clinical score; if ≥6 → PYP scintigraphy with concurrent monoclonal screen[3,4]
Bilateral carpal tunnel syndrome (CTS)	Precedes ATTR cardiac diagnosis by **5–10 years**;[3] high-yield red flag	**Document bilaterality**; echocardiogram; NT-proBNP; consider ATTR-CM score and PYP at any age >60 y
Degenerative aortic stenosis in patients >60 y	ATTR-CM present in up to **16%** of **symptomatic aortic stenosis**[3]	Concurrent ATTR evaluation in symptomatic aortic stenosis; relevant to TAVR decision-making and medical therapy
Monoclonal gammopathy of undetermined significance (MGUS)	Relative risk of AL amyloidosis 8.8; **1% incidence in MGUS** cohort of 1,384 patients[21]	Annual monoclonal screen; proactive organ-screening review (urine protein, NT-proBNP, autonomic symptoms)
Multiple myeloma	**10–15%** of myeloma patients develop AL amyloidosis;[2] 38% have Congo red–positive deposits in fat or marrow	**Proactive amyloidosis screening** in myeloma patients with organ dysfunction (HF, proteinuria, neuropathy)

CONDITION	PREVALENCE/ ASSOCIATION[2–4,16]	SCREENING APPROACH[2–4,16]

ABBREVIATIONS: AA = secondary systemic amyloidosis; AL = light chain amyloidosis; ATTR = transthyretin amyloidosis; ATTR-CM = transthyretin amyloid cardiomyopathy; CTS = carpal tunnel syndrome; FLC = free light chain; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; LV = left ventricular; MGUS = monoclonal gammopathy of undetermined significance; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PYP = technetium-99m pyrophosphate; RA = rheumatoid arthritis; SIFE = serum immunofixation electrophoresis; TAVR = transcatheter aortic valve replacement; UIFE = urine immunofixation electrophoresis

Staging/Severity Matrix– Cardiac Amyloidosis Staging System

FEATURE	AL-CM: MAYO 2012 STAGING SYSTEM[14]	ATTR-CM: NAC (UK NATIONAL AMYLOIDOSIS CENTRE) STAGING SYSTEM[15]
Biomarkers used	NT-proBNP, Troponin T (or hs-TnT), dFLC	NT-proBNP, eGFR
Thresholds	NT-proBNP ≥1,800 ng/L; cTnT ≥0.025 µg/L (or hs-TnT ≥40 pg/mL); dFLC ≥18 mg/dL	NT-proBNP ≥3,000 ng/L; eGFR 45 mL/min
Stage I	0 markers above threshold	Both below threshold
Stage II	1 marker above threshold	1 marker above threshold
Stage III	2 markers above threshold	Both above threshold
Stage IV	3 markers above threshold	**Expanded NAC**:[15] NT-proBNP ≥10,000 ng/L regardless of eGFR
Medial survival (I/II/III/IV)	94.1/40.3/14/5.8 months	69.2/46.7/24.1 months
Applicability	AL amyloidosis (**all organ involvement**)	ATTRwt and ATTRv **cardiomyopathy**

ABBREVIATIONS: AL = light chain amyloidosis; CM = cardiomyopathy; ATTR = transthyretin amyloidosis; ATTR-CM = transthyretin amyloid cardiomyopathy; NAC = UK National Amyloidosis Centre; NT-proBNP = N-terminal pro-B-type natriuretic peptide; hs-TnT = high-sensitivity troponin T; dFLC = difference in involved and uninvolved free light chains; eGFR = estimated glomerular filtration rate; cTnT = cardiac troponin T; ATTRwt = wild-type transthyretin amyloidosis; ATTRv = hereditary (variant) transthyretin amyloidosis

CLINICAL PEARL — NON-CARDIAC ORGAN-SPECIFIC STAGING IN SYSTEMIC AMYLOIDOSIS

No single unified staging system captures **all organ involvement** in systemic amyloidosis; staging is modular and organ-specific, complementing the cardiac systems that drive overall survival prognostication. For the kidney in AL amyloidosis, the **Pavia Renal Staging System**[22] uses 24-hour proteinuria (>5 g/day) and eGFR (50 mL/min) to predict progression to dialysis, with 3-year dialysis risks of approximately 0%, 17%, and 60% for stages I–III.[22] For **peripheral neuropathy** in hereditary ATTR (ATTRv), the **FAP staging system** (Coutinho)[23] classifies patients by ambulatory status (**Stage 1** = ambulatory; **Stage 2** = assisted ambulation; **Stage 3** = wheelchair/bedridden) and directly guides treatment selection. Hepatic, GI, lung, and soft tissue involvement in AL amyloidosis are defined by the **International Amyloidosis Consensus Criteria**[4,6] but lack dedicated staging systems. AA amyloidosis **has no formal staging system**; prognosis is driven by sustained suppression of serum amyloid A (SAA) **below 10 mg/L**.[24] In practice, these organ-specific assessments are used in parallel with cardiac staging to characterize total disease burden and inform treatment intensity, transplant eligibility, and therapeutic goals.

RED FLAG: URGENT ACTION

Red Flag: Urgent ActionImmediate ED referral — life-threatening, act now

(**1**) **syncope or presyncope** in known or suspected cardiac amyloidosis (risk of high-grade AV block or ventricular arrhythmia); (**2**) acute decompensated **heart failure** with hypotension unresponsive to diuretics; (**3**) active bleeding in AL amyloidosis with suspected Factor X deficiency (level <25%); (**4**) symptomatic bradycardia or high-grade AV block; (**5**) ventricular tachycardia or fibrillation; (**6**) acute kidney injury with nephrotic syndrome and anasarca. Do not wait for outpatient workup

RED FLAG: RAPID DECLINE

Red Flag: Rapid DeclineUrgent same-day or next-day specialist contact

(**1**) new diagnosis of AL amyloidosis = **immediate hematology/oncology referral**; (**2**) Mayo Stage IIIb AL (NT-proBNP >8,500 ng/L + troponin elevated) = median survival **5 months** without treatment; (**3**) orthostatic hypotension refractory to conservative measures (fall/syncope risk); (**4**) rapidly progressive peripheral neuropathy with weakness or pain; (**5**) new-onset atrial fibrillation in suspected or confirmed cardiac amyloidosis; (**6**) unexplained persistent troponin and NT-proBNP elevation despite HFpEF treatment. **Expedited within days**: HFpEF with LV wall ≥14 mm plus any cluster red flag; ATTR-CM **score ≥6**; unexplained proteinuria >0.5 g/24 h without diabetes or long-standing HTN

AAVBC PERSPECTIVE

*Recognition of amyloidosis in primary care begins with **pattern awareness**, not dashboards. HFpEF with **LV wall thickness ≥14 mm** (6 to 17% ATTR-CM yield),[25] **bilateral** carpal tunnel syndrome in an older patient, lumbar spinal stenosis, spontaneous **biceps tendon rupture**, or autonomic neuropathy should raise suspicion for systemic amyloidosis. Cardiac amyloidosis staging frameworks are **more comprehensive** than those used for many non-cardiac manifestations, partly because cardiac involvement is a major driver of morbidity and mortality. Screening begins with a three-test monoclonal panel, with combined sensitivity approaching **99% for AL amyloidosis**.[4] If cardiac ATTR is suspected and the monoclonal screen is negative, 99mTc-PYP scintigraphy with Perugini grading can identify ATTR-CM. PYP should never be interpreted alone, as a monoclonal protein **must first be excluded** to avoid misdiagnosing AL amyloidosis as ATTR. Early recognition of findings often misattributed to "normal aging" and integration of this two-step diagnostic logic into clinical workflows can **shorten diagnostic delay** from years to months and connect patients to earlier **organ-preserving care**.*

3 MEAT DOCUMENTATION ESSENTIALS

Male patient, 74, with wild-type ATTR cardiac amyloidosis (E85.82) diagnosed 6 months ago. Initial workup prompted by HFpEF with LV wall thickness 16 mm, bilateral CTS documented 4 years prior, low QRS voltage on ECG, and ATTR-CM score 8. Three-test monoclonal screen (FLC, SIFE, UIFE) was negative; PYP scan Perugini grade 3; TTR gene sequencing wild-type. Presents for scheduled PCP follow-up. On tafamidis 61 mg daily × 4 months; SGLT2 inhibitor (empagliflozin) added for HFpEF. **Clinical Frailty Scale 4** (vulnerable but independent). Comorbidities: bilateral CTS s/p release × 2; lumbar spinal stenosis; type 2 diabetes on metformin; CKD Stage 3a.

MONITOR: "Cardiology labs [date]: NT-proBNP 1,680 (baseline 2,100), TnT 0.042 (baseline 0.048), Mayo ATTR-CM Stage II unchanged. TSH normal. Echo [date]: LVEF 55%, LV wall 16 mm, apical sparing on strain. 6MWD 340 m (baseline 310 m). eGFR 52 stable. Weight and orthostatics stable. Tafamidis and empagliflozin taken as prescribed, well tolerated."

EVALUATE: Stable ATTRwt-CM on tafamidis/SGLT2i. Modest biomarker and functional improvement at 4 months consistent with expected tafamidis response. No new arrhythmias, syncope, or decompensation. Frailty assessment supports treatment continuation. CKD stable; diabetes controlled.

ASSESS: "1) ATTRwt cardiac amyloidosis (**E85.82**), Stage II, on tafamidis/SGLT2i; 2) Cardiomyopathy in diseases classified elsewhere (**I43**); 3) HFpEF (**I50.32**), stable; 4) Bilateral CTS s/p release (**G56.00**); 5) Lumbar spinal stenosis (**M48.06**); 6) T2DM without complications (**E11.9**), controlled; 7)CKD Stage 3a (**N18.30**), stable"

TREAT: "Continue tafamidis 61 mg daily and empagliflozin 10 mg daily. Avoid ACEi/ARBs, CCBs, digoxin (contraindicated in amyloid CM). Continue metformin 1,000 mg BID. Pfizer bridge program active; navigation review at 6-month mark. Cardiology follow-up 3 months for serial biomarkers; amyloidosis center annually. Counseled on syncope/arrhythmia warning signs. Advance care planning initiated; healthcare proxy designated."

Clinical Documentation Elements

- **Link subtype to care pathway:** Document the **specific subtype** (E85.81 AL, E85.82 ATTRwt, E85.0 or E85.1 ATTRv, E85.3 AA, E85.4 organ-limited) because it **determines the treatment pathway**: AL = hematology/oncology chemotherapy; ATTR = cardiology + TTR stabilizer or silencer; AA = treat underlying inflammatory disease
- **Include organ involvement codes alongside E85.x:** The amyloidosis code documents the cause; **organ-specific codes document the consequence**. Heart (I43, I50.3x), kidney (N04.x nephrotic syndrome), nerve (G60.8), liver (K76.89), GI codes should be listed separately
- **Document current staging and biomarkers:** Record the most recent NT-proBNP, troponin T/I, dFLC (AL), 6-minute walk distance, and Mayo or UK NAC stage with dates. Staging drives treatment intensity and goals-of-care conversation timing; include Clinical Frailty Scale or FRAIL score
- **Record pharmaceutical assistance navigation:** Tafamidis list price **~$225,000/year**; Medicare beneficiary out-of-pocket **$12,000–$16,000/year**. Vutrisiran and acoramidis carry similar cost burdens. Pharmaceutical assistance program enrollment and status is a **care coordination responsibility**, not an administrative detail

Reframing Common Documentation Shortcuts

INSTEAD OF…	DOCUMENT…
'Amyloidosis' on problem list	'Wild-type ATTR cardiac amyloidosis (**E85.82**), Mayo ATTR-CM Stage II, on tafamidis 61 mg daily since [date]; Clinical Frailty Scale [x].' Specify subtype and stage at every encounter
'Amyloidosis, unspecified' (E85.9) after workup	**Specific subtype once confirmed**: '**E85.81** AL amyloidosis, Mayo 2004 Stage II, on Dara-CyBorD cycle 3 of 6.' Reserve E85.9 **ONLY** when tissue typing is incomplete or inconclusive
'Cardiac amyloidosis' without subtype	'Wild-type ATTR cardiac amyloidosis (**E85.82**); confirmed by PYP Perugini grade 3 AND negative monoclonal screen AND TTR gene sequencing wild-type'
'PYP positive, ATTR' without monoclonal exclusion	'Perugini grade 3 PYP uptake WITH concurrent negative FLC, SIFE, UIFE: supports **E85.82**.' Without the monoclonal exclusion, **AL cannot be ruled out**
I43 alone for amyloid cardiomyopathy	'**E85.4** (organ-limited amyloidosis) → I43 (cardiomyopathy in diseases classified elsewhere) → I50.32 (HFpEF).' Sequencing reflects disease primacy

INSTEAD OF…	DOCUMENT…

ABBREVIATIONS: AA = secondary systemic amyloidosis; AL = light chain amyloidosis; ATTR = transthyretin amyloidosis; ATTRwt = wild-type transthyretin amyloidosis; FLC = free light chain; HFpEF = heart failure with preserved ejection fraction; PYP = technetium-99m pyrophosphate; SIFE = serum immunofixation electrophoresis; TTR = transthyretin; UIFE = urine immunofixation electrophoresis

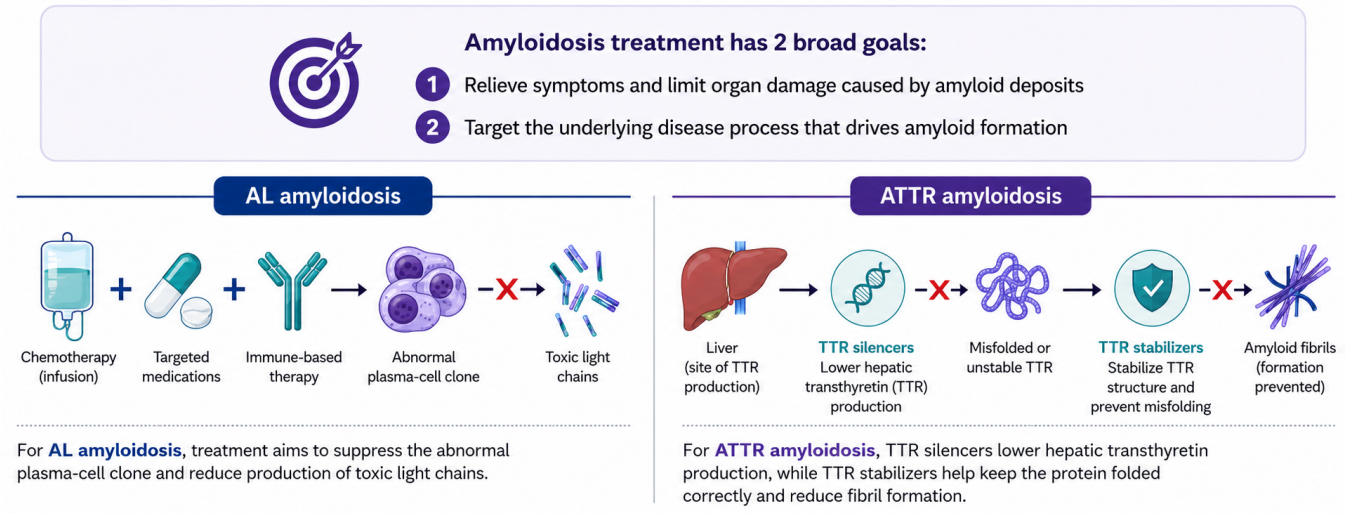
DOCUMENTATION IS COMPREHENSIVE CODING

The goal is a clinical record that accurately reflects **each patient's amyloidosis complexity**: subtype, organ involvement, stage, treatment phase, and frailty. When the note tells the clinical story well, HCC 50 mapping follows naturally as a consequence of careful subtype-specific documentation.

4 TREATMENT AND REFERRAL QUICK GUIDE

Disease-modifying therapies now exist for **both AL and ATTR amyloidosis**. **Daratumumab**-based induction (Dara-CyBorD) improves hematologic and organ responses in AL amyloidosis. TTR stabilizers (tafamidis, acoramidis) and the gene silencer **vutrisiran** reduce mortality and cardiovascular hospitalizations in **ATTR-CM**. A critical early on-ramp for patients to receive these therapies is through early disease recognition by PCPs: monoclonal screening, specialist referral, comorbidity management, and pharmaceutical assistance navigation alongside subspecialty teams.

Treatment Options: AL Amyloidosis and TTR Amyloidosis



Therapy Escalation Criteria

TRIGGER[2–4,16]	ACTION[2–4,16]
Any red flag cluster: HFpEF + LV wall ≥14 mm + low QRS voltage OR bilateral CTS OR lumbar spinal stenosis OR spontaneous biceps rupture OR macroglossia/periorbital purpura OR apical sparing strain	Initiate monoclonal screen **AND** echocardiogram with strain **AND** NT-proBNP + troponin; Apply ATTR-CM clinical score; do **NOT** order PYP alone before monoclonal screen[3,4,15]
ATTR-CM clinical score ≥6 in HFpEF patient with negative monoclonal screen	PYP scintigraphy (CPT 78451/78452); if Perugini **grade 2–3 AND** concurrent monoclonal screen confirmed negative → ATTR-CM confirmed; code E85.4 → I43 → I50.3x and refer to cardiology-amyloidosis center within 2–4 weeks; Obtain TTR gene sequencing to distinguish wild-type from variant
Any positive FLC, SIFE, or UIFE	Confirm with **full monoclonal panel**; immediate hematology/oncology referral (within 1–2 weeks); AL is aggressive: 25% of patients die within 6 months of diagnosis without treatment
New diagnosis of AL amyloidosis (E85.81)	Same-day or next-day hematology/oncology contact for Dara-CyBorD initiation planning, Mayo staging (troponin T + NT-proBNP + dFLC), and organ-function baselines; Frailty assessment (Clinical Frailty Scale or FRAIL) before induction
Confirmed ATTRv (E85.0 or E85.1) in patient or family member	Confirm neuropathic (**E85.1**) or non-neuropathic (**E85.0**); Referral to hereditary amyloidosis center for genetic counseling and **cascade testing**; V122I (African American, 10% penetrance at 65 rising to 39% by 80 y);[12] V30M (Portuguese ~80%, Swedish ~11% penetrance = ancestry-specific); consider vutrisiran

ABBREVIATIONS: ATTR = transthyretin amyloidosis; ATTR-CM = transthyretin amyloid cardiomyopathy; ATTRv = hereditary/variant transthyretin amyloidosis; CTS = carpal tunnel syndrome; CPT = current procedural terminology; dFLC = difference in involved and uninvolved free light chain; ED = emergency department; FLC = free light chain; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; LV = left ventricular; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PYP = technetium-99m pyrophosphate; SIFE = serum immunofixation electrophoresis; TTR = transthyretin; UIFE = urine immunofixation electrophoresis; V122I = Val122Ile TTR variant; V30M = Val30Met TTR variant

NCCN/ACC/AHA Aligned Recommendations

CATEGORY[2–4,16]	RECOMMENDED AGENT/ APPROACH[2–4,16]	NOTES[2–4,16]
AL amyloidosis : first-line (Mayo Stage I–IIIa)	Dara-CyBorD (daratumumab + bortezomib + cyclophosphamide + dexamethasone)	NCCN 2026 Category 1; FDA-approved 2021 (**ANDROMEDA trial**);[26] SC daratumumab preferred for volume-sensitive cardiac amyloidosis; SC bortezomib preferred (lower neuropathy); goal: **complete hematologic response**
AL amyloidosis: second-line	Bortezomib-based regimens (if not used first-line); **ixazomib/dex**; pomalidomide/dex (avoid in advanced cardiac involvement); lenalidomide (avoid in advanced cardiac/autonomic involvement); venetoclax	**Carfilzomib**: avoid in cardiac amyloidosis; Autologous SCT eligible in ~20–25% of AL patients (select Mayo Stage I–II)
ATTR cardiac amyloidosis: TTR stabilizer first-line	tafamidis (Vyndamax)	**ATTR-ACT trial**:[27] 30% reduction in all-cause mortality, 32% reduction in CV hospitalizations over 30 months; NYHA Class I–III; **Pharmaceutical assistance navigation recommended** (high cost)
ATTR cardiac amyloidosis: TTR stabilizer alternative	acoramidis (Attruby)	**ATTRibute-CM trial**:[28] demonstrated efficacy with favorable safety profile
ATTR cardiac amyloidosis: TTR gene silencer	vutrisiran (Amvuttra)	**HELIOS-B trial**:[29] reduction in CV mortality and hospitalizations; FDA-approved for **ATTR polyneuropathy and ATTR-CM;** requires vitamin A supplementation

ABBREVIATIONS: ACC = American College of Cardiology; AHA = American Heart Association; AL = light chain amyloidosis; ARB = angiotensin II receptor blocker; ATTR = transthyretin amyloidosis; ATTR-ACT = Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; ATTR-CM = transthyretin amyloid cardiomyopathy; CV = cardiovascular; Dara-CyBorD = daratumumab/cyclophosphamide/bortezomib/dexamethasone; ESC = European Society of Cardiology; FDA = Food and Drug Administration; FLC = free light chain; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; IV = intravenous; MRA = mineralocorticoid receptor antagonist; NCCN = National Comprehensive Cancer Network; NYHA = New York Heart Association; OOP = out-of-pocket; PO = by mouth; SC = subcutaneous; SGLT2 = sodium-glucose cotransporter 2; TTR = transthyretin

Non-Pharmacologic Treatment and Lifestyle Modification

INTERVENTION	TARGET/RECOMMENDATION[2–4,16]	NOTES[2–4,16]
Frailty assessment before therapy initiation	Clinical Frailty Scale OR FRAIL scale OR Comprehensive Geriatric Assessment (CGA) at diagnosis and reassessed every 6 months	Frailty, **not chronological age**, guides treatment intensity;[4,30] frailty is dynamic; effective hematologic control in AL can improve frailty score
Advance care planning: initiated at diagnosis, not deferred	Goals-of-care conversation at diagnosis; healthcare proxy designation; palliative care integration concurrent with disease-modifying therapy	AL Stage IIIb (median survival 5 months untreated) and late-stage ATTR-CM warrant **early palliative care**, not end-of-life only
Pharmaceutical assistance program navigation	Enrollment coordination **at prescription initiation**: Pfizer bridge for tafamidis; BridgeBio assistance for acoramidis; Alnylam assistance for vutrisiran; Janssen Johnson & Johnson Patient Assistance for daratumumab	Medicare beneficiaries face **$12,000–$16,000/year OOP** for ATTR therapies:[2] navigation is a **care coordination responsibility** equivalent to the prescription itself
Autonomic and supportive care for neuropathy	**Orthostatic hypotension**: **midodrine preferred; AVOID** fludrocortisone (fluid retention in cardiac amyloidosis); **Gastroparesis**: prokinetics; **diarrhea**: loperamide, octreotide; **neuropathic pain**: gabapentin, pregabalin, duloxetine; AVOID **tricyclic antidepressants** (urinary retention, worsening orthostasis)	Autonomic management is a chronic care task **shared** between PCP and neurology/cardiology; document response at each visit
Medication reconciliation with amyloid-specific contraindications	**AVOID** at every encounter: ACE inhibitors, ARBs, calcium channel blockers, digoxin, verapamil, diltiazem, carfilzomib (AL patients), fludrocortisone; CAUTION with loop diuretics (preload sensitivity) and NSAIDs	Older adults with amyloidosis frequently have multiple comorbidities (CKD, HF, autonomic neuropathy, diabetes); standard cardiac and antihypertensive medications **are dangerous**[2]

ABBREVIATIONS: ACE = angiotensin-converting enzyme; AL = light chain amyloidosis; ARB = angiotensin II receptor blocker; ATTR = transthyretin amyloidosis; ATTR-CM = transthyretin amyloid cardiomyopathy; ATTRv = hereditary/variant transthyretin amyloidosis; CGA = comprehensive geriatric assessment; CKD = chronic kidney disease; CTS = carpal tunnel syndrome; HF = heart failure; NSAID = nonsteroidal anti-inflammatory drug; OOP = out-of-pocket; PCP = primary care provider; SDOH = social determinants of health; TTR = transthyretin

Medication Safety and Dose Adjustments – Key Interactions for Systemic Amyloidosis

AGENT/CLASS*	INTERACTION/ MECHANISM	RISK LEVEL	ADJUSTMENT*[2–4,16]	MONITORING*
ACE inhibitors, ARBs	Autonomic dysfunction + fixed cardiac output → **severe hypotension**	HIGH (AVOID)	**Discontinue** at diagnosis; use SGLT2i/MRAs for HF instead	Orthostatic vitals each visit
CCBs, digoxin	**CCBs**: negative inotropy in restrictive CM; **digoxin**: binds amyloid fibrils → toxicity at therapeutic levels	HIGH (AVOID)	**Deprescribe** at diagnosis; do not initiate	Digoxin levels **unreliable** in amyloidosis
Carfilzomib	Increased cardiac/ pulmonary toxicity in amyloid CM vs. myeloma	HIGH (AVOID in cardiac AL)	Avoid; use bortezomib, ixazomib, or alternatives	If used: serial NT-proBNP, troponin
dexamethasone (Dara-CyBorD in AL)	Poorly tolerated in frail/elderly; worsens hyperglycemia, fluid retention, delirium	MODERATE – HIGH	Dose reduction if age >70, BMI 18.5, hypervolemia, or uncontrolled diabetes	Glucose, weight, fluid status, mood each cycle
bortezomib (Dara-CyBorD)	Additive neurotoxicity with preexisting neuropathy	MODERATE – HIGH	SC preferred over IV; weekly dosing; dose reduce/hold for ≥Grade 2 neuropathy	Neuropathy assessment each cycle
tafamidis (Vyndamax) long-term use	Emerging post-market AE signals in older adults (FAERS data)	LOW – MODERATE (MONITOR)	No dose adjustment; discontinue if NYHA Class IV or significant AE	NT-proBNP/troponin q3–6 months; annual echo with strain, 6MWT
vutrisiran (Amvuttra)	TTR knockdown reduces retinol-binding protein → vitamin A deficiency	MODERATE (requires supplementation)	Vitamin A supplementation required per FDA label	Annual serum vitamin A; evaluate vision changes promptly

AGENT/CLASS*	INTERACTION/ MECHANISM	RISK LEVEL	ADJUSTMENT*[2–4,16]	MONITORING*

ABBREVIATIONS: ACE = angiotensin-converting enzyme; AE = adverse event; AL = light chain amyloidosis; ARB = angiotensin II receptor blocker; CCB = calcium channel blocker; CM = cardiomyopathy; Dara-CyBorD = daratumumab/cyclophosphamide/bortezomib/dexamethasone; FAERS = FDA Adverse Event Reporting System; FDA = Food and Drug Administration; HF = heart failure; IV = intravenous; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; SC = subcutaneous; SGLT2i = sodium-glucose cotransporter 2 inhibitor; TTR = transthyretin; 6MWT = 6-minute walk test
**consult FDA labels for the most up-to-date dosage information, contraindications, and drug-drug interactions*

When to Refer

CRITERION[2–4,16]	SPECIALIST	URGENCY
Any positive FLC, SIFE, or UIFE	Hematology/oncology with amyloidosis expertise	Within 1–2 weeks. AL is aggressive: 25% die within 6 months of diagnosis without treatment
ATTR-CM clinical score ≥6 in HFpEF with negative monoclonal screen	Cardiology-amyloidosis center (for PYP interpretation and disease-modifying therapy)	Within 2–4 weeks; PYP is the confirmatory test; do not delay referral awaiting PYP completion
Confirmed ATTR-CM (E85.82 or E85.4 → I43)	Amyloidosis center + cardiology	Within 2 weeks for disease-modifying therapy initiation (tafamidis/acoramidis/vutrisiran) and pharmaceutical assistance navigation
Confirmed ATTRv (E85.0 or E85.1) in patient or suspected in family member	Hereditary amyloidosis center + genetic counseling	Within 4 weeks for confirmatory genetic testing, cascade testing planning, and neurology evaluation if polyneuropathy (E85.1)
AL amyloidosis Mayo Stage IIIb (NT-proBNP >8,500 ng/L + troponin elevated) OR any decompensation	Hematology/oncology emergency + palliative care	IMMEDIATE; dose-modified Dara-CyBorD or single-agent daratumumab; ACP conversation at first contact

ABBREVIATIONS: ACP = advance care planning; AL = light chain amyloidosis; ATTR = transthyretin amyloidosis; ATTR-CM = transthyretin amyloid cardiomyopathy; ATTRv = hereditary/variant transthyretin amyloidosis; CFS = Clinical Frailty Scale; FLC = free light chain; HFpEF = heart failure with preserved ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PYP = technetium-99m pyrophosphate; SIFE = serum immunofixation electrophoresis; UIFE = urine immunofixation electrophoresis

Follow-Up Timing

STAGE/CATEGORY[2–4,16]	FREQUENCY	LABS/ASSESSMENTS TO MONITOR[2–4,16]
AL amyloidosis on Dara-CyBorD induction (cycles 1–6)	Every **2–4 weeks** with hematology; PCP every 4–8 weeks for comorbidity management	FLC (kappa, lambda, ratio, dFLC); SPEP/UIFE for M-protein; CBC; CMP; NT-proBNP; troponin; glucose (dexamethasone effect); weight and fluid status; neuropathy inventory (bortezomib)
AL amyloidosis post-induction/ maintenance	Every **3 months** with hematology; PCP every 3–6 months	FLC and M-protein (hematologic response monitoring); NT-proBNP and troponin (cardiac response); annual echocardiogram; organ-specific monitoring
ATTRwt on tafamidis or acoramidis	Cardiology every **3–6 months**; amyloidosis center annually; PCP every 3–6 months	NT-proBNP and troponin every 3–6 months; annual echocardiogram with strain; 6-minute walk distance; TSH (tafamidis); ECG (conduction disease surveillance)
ATTR on vutrisiran (quarterly SC)	Every **3 months** with cardiology (timed with dosing); PCP every 3–6 months	Serum vitamin A annually; ophthalmology if vision changes; NT-proBNP and troponin; TTR levels per protocol; annual functional assessment
ATTRv: patient in active follow-up + cascade testing ongoing in family	Cardiology and neurology every **6 months**; genetic counseling per family progress; PCP annually for family history update	NT-proBNP, troponin, echocardiogram with strain; EMG/NCS for new neuropathy symptoms; autonomic testing; **cascade status tracking**

ABBREVIATIONS: AA = secondary systemic amyloidosis; AL = light chain amyloidosis; ATTR = transthyretin amyloidosis; ATTRv = hereditary/variant transthyretin amyloidosis; ATTRwt = wild-type transthyretin amyloidosis; CBC = complete blood count; CDAI = Clinical Disease Activity Index (RA) OR Crohn's Disease Activity Index; CMP = comprehensive metabolic panel; CRP = C-reactive protein; Dara-CyBorD = daratumumab/cyclophosphamide/bortezomib/dexamethasone; DAS28 = Disease Activity Score 28; dFLC = difference in involved and uninvolved free light chain; ECG = electrocardiogram; EMG = electromyography; FLC = free light chain; GI = gastroenterology; NCS = nerve conduction study; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PCP = primary care provider; RA = rheumatoid arthritis; SAA = serum amyloid A; SC = subcutaneous; SPEP = serum protein electrophoresis; TSH = thyroid-stimulating hormone; TTR = transthyretin; UIFE = urine immunofixation electrophoresis

Comorbidity Management

COMORBIDITY	APPROACH[2–4,16]	CAUTION[2–4,16]
Heart failure with preserved ejection fraction (HFpEF)	**SGLT2 inhibitors** (empagliflozin, dapagliflozin) and MRAs (spironolactone, eplerenone) first-line; Loop diuretics titrated carefully for volume management	**AVOID** ACE inhibitors, ARBs, CCBs, digoxin in cardiac amyloidosis: different rules from standard HFpEF[3,6]

COMORBIDITY	APPROACH[2–4,16]	CAUTION[2–4,16]
Atrial fibrillation in cardiac amyloidosis	Anticoagulation decisions **individualized**; DOAC preferred over warfarin in most patients without valve disease; rate control with cautious beta-blocker titration (amyloid hearts are preload-sensitive)	Factor X deficiency risk in AL (active bleeding with level <25% warrants immediate evaluation); isolated atrial amyloidosis is established cause of AF in elderly[31]
Chronic kidney disease	AL amyloidosis renal involvement ~70%; nephrotic syndrome common; nephrology co-management	Standard CKD-HTN algorithms **do not apply** in cardiac amyloidosis; DAA-like renal adjustments not a consideration here; focus is ACP and **organ preservation**
Type 2 diabetes mellitus	Metformin + GLP-1 RA (semaglutide, tirzepatide) preferred; metformin dose-adjust for CKD	Dexamethasone (AL induction) worsens glycemic control; consider more frequent glucose monitoring during Dara-CyBorD cycles
Monoclonal gammopathy of undetermined significance (MGUS)	Annual monoclonal screen; clinical review for organ dysfunction suggestive of AL progression	Relative risk of AL amyloidosis 8.8: do not treat MGUS as benign; 1% incidence of AL in MGUS cohorts[21]

ABBREVIATIONS: ACE = angiotensin-converting enzyme; ACP = advance care planning; AF = atrial fibrillation; AL = light chain amyloidosis; ARB = angiotensin II receptor blocker; CCB = calcium channel blocker; CKD = chronic kidney disease; DAA = direct-acting antiviral; Dara-CyBorD = daratumumab/cyclophosphamide/bortezomib/dexamethasone; DOAC = direct oral anticoagulant; FLC = free light chain; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HTN = hypertension; MGUS = monoclonal gammopathy of undetermined significance; MRA = mineralocorticoid receptor antagonist; SGLT2 = sodium-glucose cotransporter 2; SIFE = serum immunofixation electrophoresis; UIFE = urine immunofixation electrophoresis

Cost-Smart Options

BRAND (EST. COST)[25,32,33]	GENERIC/ ALTERNATIVE (EST. COST)[25,32,33]	EST. SAVINGS	COST-SMART TIP[25,32,33]
tafamidis (Vyndamax/ Vyndaqel) ~$225,000/ year list price; $12,000–$16,000 Medicare OOP	**No generic available**	N/A	**Pfizer bridge/patient assistanc**e for qualifying Medicare beneficiaries
acoramidis (Attruby) ~$240,000/year list price	**No generic available**	N/A	**BridgeBio patient assistance program**; reduced copay and potential price reductions for eligible patients

BRAND (EST. COST)[25,32,33]	GENERIC/ ALTERNATIVE (EST. COST)[25,32,33]	EST. SAVINGS	COST-SMART TIP[25,32,33]
vutrisiran (Amvuttra) brand-only ~$470,000/year list price	**No generic available**	N/A	**Alnylam Assist patient assistance**; quarterly SC dosing may improve adherence vs. daily tafamidis; vitamin A supplementation requirement adds minor cost
Daratumumab (Darzalex/ Darzalex Faspro) IV or SC for AL ~$135,000-190,000/ year list price	**No generic available**; IV and SC formulations available	SC may reduce infusion center costs; Part B vs. Part D billing differs	**Janssen (J & J) Patient Assistance**; SC preferred for volume-sensitive cardiac AL (reduced infusion reactions); Coverage: IV Part B (outpatient infusion); SC Part D

ABBREVIATIONS: AL = light chain amyloidosis; ATTR = transthyretin amyloidosis; Dara-CyBorD = daratumumab/ cyclophosphamide/bortezomib/dexamethasone; FDA = Food and Drug Administration; IV = intravenous; OOP = out-of-pocket; SAE = serious adverse event; SC = subcutaneous

Patient Education and Adherence

Patients should know the warning signs warranting urgent evaluation: **syncope or near-syncope** (possible arrhythmia or AV block → ED); sudden worsening of **shortness of breath** with leg swelling (acute decompensation → same-day contact); **active bleeding** with easy bruising (possible Factor X deficiency in AL → urgent evaluation); new **confusion or falls** (orthostatic hypotension, medication effect, or decompensation → prompt evaluation); rapidly progressive neuropathy (ATTRv → neurology). Tafamidis, acoramidis, and vutrisiran adherence is foundational to disease modification: set up pharmacy auto-refill, **confirm pharmaceutical assistance enrollment**, and counsel on vitamin A supplementation for vutrisiran. Dara-CyBorD adherence requires coordinated infusion center scheduling; herpes zoster prophylaxis is standard with daratumumab or bortezomib.

Quality Metrics Tie-In: None Currently for Systemic Amyloidosis

MEASURE	STANDARD	NOTES
Amyloidosis-specific quality measures (HEDIS 2025/CMS Star 2025)	**No condition-specific measure exist:** amyloidosis is too rare for population-level metrics	Patients captured in related HF measures (Plan All-Cause Readmissions), CKD/KED, and Medication Reconciliation Post-Discharge (MRP); diagnostic screening and advance care planning is not a current Star measure but **is a VBC priority**

QUALITY OUTCOME

Raised **index of suspicion**, structured three-test monoclonal screening, ATTR-CM clinical scoring in HFpEF, subtype-specific coding, and **proactive pharmaceutical assistance navigation** each reflect the same underlying principle: the right clinical work, done early and documented clearly, drives both care quality and measured outcomes. Where no national Star or HEDIS measure exists (as is the case for amyloidosis in 2026), **internal VBC metrics** aligned to NCCN, ACC, AHA, and JACC Frailty guideline endpoints sustain the care quality the national measures **may eventually reflect**.

DOCUMENTATION

For every patient with active amyloidosis during the reporting year, the PCP note should confirm

- **Specific** subtype code (E85.81 AL, E85.82 ATTRwt, E85.0 or E85.1 ATTRv, E85.3 AA, or E85.4 organ-limited; **E85.9 only when justified**)
- Organ involvement codes alongside (heart I43/I50.3x, kidney N04.x, nerve G60.8, liver K76.89, GI codes),
- Current stage (Mayo 2004/2012 for AL, Mayo ATTR-CM or UK NAC for ATTR) with biomarker values and dates
- Treatment phase plus frailty (CFS or FRAIL) with pharmaceutical assistance program status.

5 CODING REMINDERS AND CASE EXAMPLES

Documentation Specificity

- **Stage/Severity:** Specify subtype (AL, ATTRwt, ATTRv, AA) **AND** affected organs **AND** stage. **For AL**: Mayo 2004 Stage I/II/III/IIIa/IIIb using NT-proBNP, troponin, and dFLC; for ATTR-CM: Mayo ATTR-CM Stage I/II/III (NT-proBNP + eGFR)[14] or UK NAC stages.[19] Document functional class (NYHA I–IV) and Clinical Frailty Scale where applicable
- **Etiology:** Use **subtype-specific codes rather than E85.9**. E85.81 = AL (light-chain); E85.82 = ATTRwt (wild-type); E85.0 or E85.1 = ATTRv neuropathic; E85.4 = organ-limited amyloidosis (including ATTR-CM when wild-type not established); E85.3 = AA (secondary to inflammatory disease); E85.9 reserved ONLY for incomplete workup. **Unspecified codes should not persist** once a subtype is established by biopsy, PYP, or genetic testing

- **Current status:** Most recent NT-proBNP, troponin (I or T), FLC ratio, 24-hour urine protein, eGFR, and echocardiogram with global longitudinal strain (apical sparing pattern). **Update every encounter** during the reporting year. For ATTR on disease-modifying therapy, document 6MWT and KCCQ score annually. For AL on Dara-CyBorD, document hematologic response (CR, VGPR, PR) per Mayo 2012 criteria[18]
- **Associated conditions:** Cardiac involvement (I43 in diseases classified elsewhere, sequenced **AFTER** E85.x; I50.3x for HFpEF), chronic kidney disease (N18.x stage-specific), peripheral neuropathy (G63 in diseases classified elsewhere), autonomic neuropathy (G90.09), and for AL, any concurrent plasma cell disorder (C90.x multiple myeloma, D47.2 MGUS). Each carries independent clinical and coding significance; **always sequence E85.x FIRST** when documenting cardiac amyloidosis
- **Chronicity: Date of biopsy or PYP-confirmed diagnosis;** duration of disease-modifying therapy (tafamidis months, Dara-CyBorD cycles completed); trajectory of NT-proBNP, eGFR, and functional status. Distinguishes active disease from stable/plateau phase. Amyloidosis is a chronic, progressive condition: **history-of codes (Z87.x) do NOT apply**. Continue E85.x coding indefinitely while disease-modifying therapy continues

Annual Clinical Review and Confirmation

- **Annual review:** All amyloidosis codes (E85.1, E85.3, E85.4, E85.81, E85.82, E85.9) must be reassessed face-to-face or via synchronous audio-video telehealth each reporting year. Update subtype confirmation, organ involvement, stage, treatment phase, and functional status
- **Clinical context:** Under CMS-HCC V28,[15] all E85.x codes map to **HCC 50** at RAF (CNA) ~0.648. The goal is **accurate clinical complexity representation**, not code optimization
- **Avoid rollover:** Do not copy last year's amyloidosis note forward without **updating biomarkers**, functional status, treatment response (or discontinuation), and **shared-decision-making conversations**. Frailty and goals of care shift = reassess at each annual visit

Good Documentation is Comprehensive Coding

EHR SHORTCUT/RISK	PREFERRED DOCUMENTATION LANGUAGE
'Amyloidosis' or 'amyloid' on problem list	'Wild-type ATTR cardiac amyloidosis (E85.82), Mayo ATTR-CM Stage II, on tafamidis 61 mg daily since [date], CFS 4.' Specify subtype and stage at every encounter
Using E85.9 (unspecified) when subtype is known	Most common amyloidosis **coding error**: wrong/ambiguous code may signal wrong care pathway; use E85.81 (AL), E85.82 (ATTRwt), E85.0 or E85.1 (ATTRv), or E85.3 (AA) when confirmed

EHR SHORTCUT/RISK	PREFERRED DOCUMENTATION LANGUAGE
Omitting organ involvement codes alongside E85.x	The amyloidosis code documents the cause; organ-specific codes **document the consequence**; heart, kidney, nerve, liver, GI codes should be listed alongside E85.x for accurate clinical representation and care coordination
'PYP positive, ATTR' without monoclonal exclusion	'Perugini grade 3 PYP uptake WITH concurrent negative FLC, SIFE, UIFE: supports E85.82.' Without monoclonal exclusion, AL cannot be ruled out
'Amyloidosis, unspecified' (E85.9) by default	Specific subtype: 'E85.81 AL amyloidosis, Mayo 2004 Stage IIIa, on Dara-CyBorD cycle 3 of 6, hematologic VGPR.' Reserve E85.9 ONLY for **incomplete workup cases**
I43 alone for cardiac amyloidosis	'E85.82 wild-type ATTR amyloidosis → I43 cardiomyopathy in diseases classified elsewhere → I50.32 HFpEF.' **Sequence (disease primacy) must be accurately documented**
'Amyloidosis secondary to RA' without both codes	'M05.79 rheumatoid arthritis with rheumatoid factor without complications; E85.3 secondary systemic amyloidosis; N04.9 nephrotic syndrome.' Both the underlying disease and the amyloidosis must be coded
'On tafamidis, doing well'	'Wild-type ATTR cardiac amyloidosis (E85.82) on tafamidis 61 mg daily × [duration]; NT-proBNP [value] [date] (trend stable); troponin T [value]; 6-minute walk [meters]; ECG [rhythm]; pharmaceutical assistance enrollment active; next cardiology [date].' **full MEAT documented**

ABBREVIATIONS: AL = light chain amyloidosis; ATTR = transthyretin amyloidosis; ATTR-CM = transthyretin amyloid cardiomyopathy; ATTRwt = wild-type transthyretin amyloidosis; CFS = Clinical Frailty Scale; Dara-CyBorD = daratumumab/cyclophosphamide/bortezomib/dexamethasone; ECG = electrocardiogram; EHR = electronic health record; FLC = free light chain; HFpEF = heart failure with preserved ejection fraction; I43 = cardiomyopathy in diseases classified elsewhere; I50.32 = HFpEF code; MEAT = monitor/evaluate/assess/treat; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PYP = technetium-99m pyrophosphate; RA = rheumatoid arthritis; SIFE = serum immunofixation electrophoresis; TTR = transthyretin; UIFE = urine immunofixation electrophoresis; VGPR = very good partial response

Brief Case Examples

SUCCESS: COMPREHENSIVE DOCUMENTATION

SCENARIO

74-year-old male with wild-type ATTR cardiac amyloidosis, Mayo ATTR-CM Stage II, on tafamidis and empagliflozin. CFS 4 (vulnerable but independent). Comorbidities: HFpEF, bilateral CTS s/p release, lumbar spinal stenosis, T2DM, CKD 3a.

Documentation: "Wild-type ATTR cardiac amyloidosis (**E85.82**); confirmed PYP Perugini grade 3 + negative FLC/SIFE/UIFE + TTR gene sequencing wild-type. Mayo ATTR-CM Stage II, unchanged. NT-proBNP **1,680 pg/mL** (down from 2,100), troponin T 0.042 ng/mL (stable), 6-minute walk 340 m (up from 310). Echo: LVEF 55%, LV wall 16 mm, apical sparing. **Tafamidis 61 mg** daily since [date]; empagliflozin 10 mg daily. ACE/ARB/CCB/digoxin **discontinued** at diagnosis. CFS 4. **Pfizer bridge enrolled**, OOP $13,800/yr. ACP complete, healthcare proxy designated. Organ codes: I43, I50.32,

G56.00, M48.06, E11.9, N18.30; sequenced E85.82 → I43 → I50.32. Cardiology-amyloidosis follow-up 3 months. MEAT documented."

Outcome: HCC 50 RAF 0.648 ≈$6,740/year in risk-adjusted care resources

PITFALL: INSUFFICIENT DOCUMENTATION

Documentation as written: "Hx of amyloidosis. HFpEF, doing okay on Lasix and lisinopril. BP 98/62. Continue current meds. F/u 6 months."

Consequence: (**1**) "Hx of" framing risks Z87.89 or E85.9 default: no subtype identified. (**2**) No staging, biomarkers, frailty score, or pharmaceutical assistance status. (**3**) Lisinopril (ACE inhibitor) is contraindicated in amyloid cardiomyopathy; BP 98/62 is consistent with the expected symptomatic hypotension. (**4**) No organ involvement codes sequenced. (5) No cardiology-amyloidosis or hematology/oncology follow-up documented. MEAT elements H-1, H-2, H-3, H-6, H-7, H-8 all missed.

RAF Impact: HCC 50 RAF 0.648 **not mapped** ≈$6,740/year in unrepresented care resources

Fix: "Wild-type ATTR cardiac amyloidosis (**E85.82**); confirmed 18 months ago by PYP grade 3 + negative FLC/SIFE/UIFE + TTR gene sequencing wild-type. Mayo ATTR-CM Stage III. NT-proBNP **6,240 pg/mL** [date] (up from 5,100), troponin T 0.082 ng/mL. CFS 5 = mildly frail. **Tafamidis 61 mg** daily. Discontinued lisinopril today (contraindicated); starting empagliflozin 10 mg daily; furosemide 20 mg continued with careful titration. Organ codes: I43, I50.32, E66.9 = sequenced **E85.82 → I43 → I50.32**. **Pfizer bridge active**, OOP reviewed. ACP complete, healthcare proxy designated. Cardiology-amyloidosis follow-up 2 weeks given Stage III progression. MEAT documented."

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