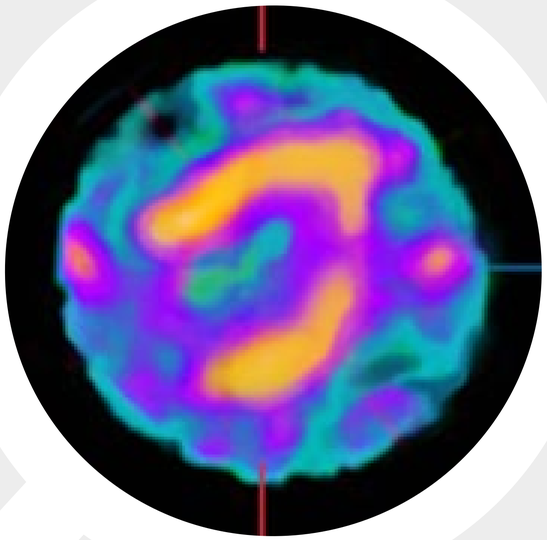


Confirming a Diagnosis of ATTR-CM With Nuclear Scintigraphy

Adapted from ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI* Expert Consensus Recommendations for Multimodality Imaging in Cardiac Amyloidosis: Evidence Base and Standardized Methods of Imaging and Diagnostic Criteria and Appropriate Utilization, Parts 1 and 2, including 2021 addendum

*The consensus report was written by a writing group of experts in cardiovascular imaging and amyloidosis assembled by the American Society of Nuclear Cardiology and endorsed by 8 societies including the American College of Cardiology, American Heart Association, American Society of Echocardiography, European Association of Nuclear Medicine, Heart Failure Society of America, International Society of Amyloidosis, Society of Cardiovascular Magnetic Resonance, and Society of Nuclear Medicine and Molecular Imaging.[1,2]

An underdiagnosed, progressive, infiltrative disease that can often be overlooked as a cause of heart failure[3]

Early diagnosis and treatment of ATTR-CM are critical, as prognosis worsens rapidly with continued amyloid deposition, subsequent advancing organ dysfunction, and significant reduction in quality of life.[3,4]

Median survival

Advanced-stage ATTR-CM in untreated patients is associated with serious cardiac complications and worse median survival[3,5]:

Once diagnosed, untreated patients with ATTR-CM have a median survival of approximately 2 to 3.5 years[4]

Early, accurate diagnosis of ATTR-CM may benefit patient care and lead to improved patient outcomes[3]

Normal, healthy heart vs the thickened walls of an ATTR amyloidosis heart

Normal heart

ATTR amyloidosis heart

Illustrative representation.

ATTR, transthyretin amyloid fibril protein.

Consider the following clinical clues, especially in combination, that raise suspicion for ATTR-CM and the need for further testing

Heart failure with preserved ejection fraction (HFpEF) or other cardiac conditions (eg, severe aortic stenosis [AS],* arrhythmias) in patients typically over the age of 60[6-8]

Intolerance to standard heart failure therapies, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and beta blockers[9]

Discordance between QRS voltage on electrocardiography (ECG) and left ventricular (LV) wall thickness[10,11]

Diagnosis of orthopaedic conditions, including carpal tunnel syndrome, lumbar spinal stenosis, biceps tendon rupture, and/or hip and knee arthroplasty[12-15]

Echocardiography showing **increased LV wall thickness**[10]

Nervous system dysfunction, including polyneuropathy and autonomic dysfunction, including gastrointestinal complaints and/or unexplained weight loss[16]

*Notably those with low-flow, low-gradient AS pattern.[9]

When ATTR-CM is suspected, diagnosis can be made noninvasively with nuclear scintigraphy and testing to rule out AL amyloidosis[17,18]

Nuclear scintigraphy with ^{99m}Tc-PYP/^{99m}Tc-MDP/^{99m}Tc-HMDP provides a unique myocardial uptake pattern in amyloid[1]

- May identify ATTR deposits early in the course of disease[1]
- Studies comparing ^{99m}Tc-PYP*/^{99m}Tc-MDP/^{99m}Tc-HMDP scintigraphy with endomyocardial biopsy (EMB) found that bone radiotracers have avidity for ATTR deposits, whereas avidity for AL cardiac amyloid deposits is minimal or absent[1]
- SPECT imaging is required in all studies (irrespective of time between injection and scan) to ensure direct visualization of tracer uptake in the myocardium.[1]

Nuclear scintigraphy should be used to facilitate early diagnosis of ATTR-CM in patients with any of the following[1]:

- Unexplained increased LV wall thickness
- HFpEF
- Familial amyloid polyneuropathy
- Family history of amyloidosis
- Low-flow, low-gradient degenerative aortic stenosis in the elderly
- History of bilateral carpal tunnel syndrome

^{99m}Tc-MDP, ^{99m}technetium-labelled methylene diphosphonate; ^{99m}Tc-HMDP, ^{99m}technetium-labelled hydroxymethylene diphosphonate; ^{99m}Tc-PYP, ^{99m}technetium-labelled pyrophosphate; AL, immunoglobulin light chain amyloidosis.
Adapted from ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI Expert Consensus Recommendations.[1,2]

Sensitivity and specificity of nuclear scintigraphy for ATTR-CM

Multiple studies have demonstrated high sensitivity and specificity[19]

- A recent meta-analysis of 6 studies of nuclear scintigraphy using technetium-labelled bone radiotracers pooling 529 patients with ATTR-CM estimated[19]:

92.2%
sensitivity

95.4%
specificity

Nuclear scintigraphy is a noninvasive, widely available diagnostic tool with high sensitivity and specificity for ATTR-CM when combined with testing to rule out AL amyloidosis.[1,17,18]

Diagnosis of ATTR-CM confirmed using visual analysis (visual grading score of ≥2 was considered positive for ATTR-CM).[18]
Adapted from ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI Expert Consensus Recommendations.[1,2]

Multisocietal expert consensus recommendations for diagnosing ATTR-CM with nuclear scintigraphy[1]

Important considerations for the acquisition of ^{99m}Tc-PYP/^{99m}Tc-MDP/^{99m}Tc-HMDP nuclear scintigraphy images

- A variety of bone radiotracers have avidity for amyloid deposits[1]: ^{99m}Tc-PYP/^{99m}Tc-MDP/^{99m}Tc-HMDP
- Both planar and SPECT imaging should be evaluated using visual interpretation and semiquantitative visual grading irrespective of the timing of acquisition[1]
- Nuclear scintigraphy should be performed using standard protocols. The recommended time between injection of ^{99m}Tc-PYP/^{99m}Tc-MDP/^{99m}Tc-HMDP and scan is 2 or 3 hours[1]
- Experienced centres may be proficient at 1-hour planar and SPECT imaging[1]
- 1-hour planar-only imaging is **not** recommended[1]

Nuclear scintigraphy using both planar and SPECT imaging is a noninvasive, readily available diagnostic tool with high sensitivity and specificity for ATTR-CM when combined with testing to rule out AL amyloidosis.[1,17,18]

Adapted from ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI Expert Consensus Recommendations.[1,2]

Recommendations for interpretation of ^{99m}Tc-PYP/^{99m}Tc-MDP/^{99m}Tc-HMDP in ATTR-CM[1]

Click to explore the steps below:

– STEP 1 –

Visual Interpretation

–STEP 2–

Semiquantitative Visual Grading

–STEP 3–
(when applicable)

H/CL Uptake Ratio Assessment

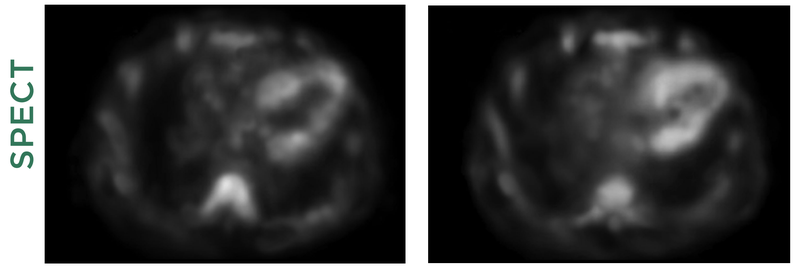
H/CL, heart-to-contralateral lung.
Adapted from ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI Expert Consensus Recommendations.[1,2]

Step 1: Visual interpretation

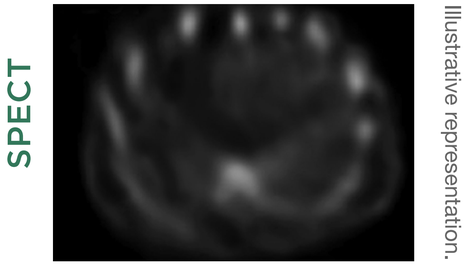
Planar and SPECT images should be evaluated to confirm diffuse radiotracer uptake in the myocardium[1]

- Use SPECT imaging to differentiate myocardial radiotracer uptake from residual blood pool activity, focal myocardial infarct, and overlapping bone (eg, from rib hot spots from fractures)[1]
- Recommend repeating SPECT at 3 hours if excess blood pool activity is noted[1]

- If myocardial tracer uptake is visually present on SPECT, proceed to step 2, semiquantitative visual grading[1]



- If no myocardial tracer uptake is present on SPECT, the visual grade is 0[1]

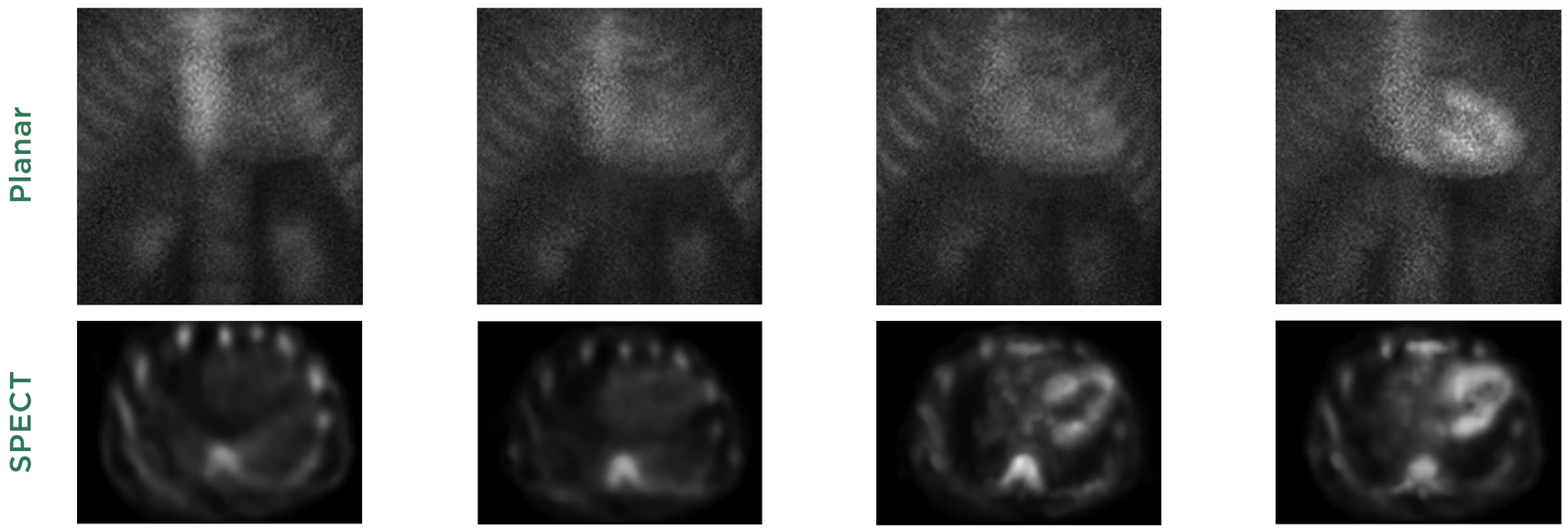


Illustrative representation.

*Written by a writing group of experts in cardiovascular imaging and amyloidosis assembled by the American Society of Nuclear Cardiology and endorsed by 9 societies including the American College of Cardiology, American Heart Association, American Society of Echocardiography, European Association of Nuclear Medicine, Heart Failure Society of America, International Society of Amyloidosis, Society of Cardiovascular Magnetic Resonance, and Society of Nuclear Medicine and Molecular Imaging.
Adapted from ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI Expert Consensus Recommendations.[1,2]

Step 2: Semiquantitative visual grading

Examine both planar and SPECT images for relative tracer uptake in the myocardium relative to ribs and grade using the following scale[1]:



Illustrative representation.

Grade 0	Grade 1	Grade 2	Grade 3
No myocardial uptake and normal bone uptake	Myocardial uptake less than rib uptake	Myocardial uptake equal to rib uptake	Myocardial uptake greater than rib uptake with mild/ absent rib uptake

- Nuclear scintigraphy with SPECT and planar imaging performed at 3 hours maximises diagnostic specificity[1]

When cardiac amyloidosis is suspected, Grade 2 or 3 myocardial uptake with concurrent testing to rule out AL is diagnostic of ATTR-CM.[1*†]

*^{99m}Tc-PYP/^{99m}Tc-MDP/^{99m}Tc-HMDP uptake could be seen in other causes of myocardial injury, including pericarditis, myocardial infarction (regional uptake), and chemotherapy- or drug-associated myocardial toxicity.[1]

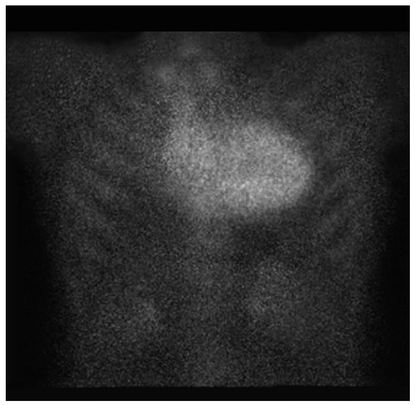
†Rule out AL: testing for presence of monoclonal protein via serum and urine immunofixation (IFE) and serum free light chain (SFLC) assay.[17]

Adapted from ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI Expert Consensus Recommendations.[1,2]

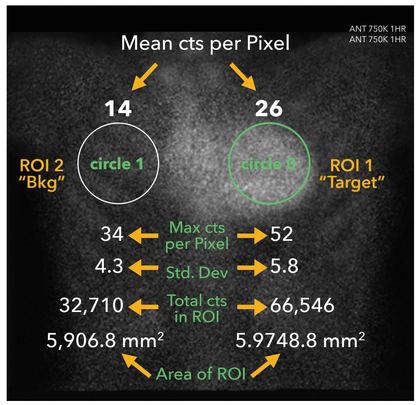
Step 3: H/CL uptake ratio assessment (when applicable)

Diagnosis of ATTR-CM cannot be made based on H/CL ratio alone. H/CL ratio is not recommended if there is absence of myocardial uptake on SPECT imaging[1]

- If the visual grade is 2 or 3, diagnosis is confirmed and H/CL ratio assessment is not necessary. H/CL ratio is typically concordant with visual grade[1]
  - If discordant or the visual grade is equivocal, H/CL ratio may be helpful to classify equivocal visual grade 1 vs 2 as positive or negative[1]
- An H/CL ratio is calculated as the fraction of heart region of interest (ROI) mean counts to contralateral lung ROI mean counts[1]
  - H/CL ratios of ≥1.5 at 1 hour can accurately identify ATTR cardiac amyloidosis if myocardial ^{99m}Tc-PYP uptake is visually confirmed on SPECT imaging and systemic AL amyloidosis is excluded[1]
- An H/CL ratio of >1.3 at 3 hours can identify ATTR cardiac amyloidosis[1]



Positive uptake[20]



H/CL = 1.86[20]

Illustrative representation.

If clinical suspicion for cardiac amyloidosis remains high despite a negative or inconclusive scintigraphy scan, consider EMB.[1]

Adapted from ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI Expert Consensus Recommendations.[1,2]

Testing to rule out AL amyloidosis

AL is a form of cardiac amyloidosis that arises from the overproduction and misfolding of monoclonal immunoglobulin light chains[1]

- Exclusion of a monoclonal process with serum and urine IFE and an SFLC assay in all patients with suspected amyloidosis is critical because it is considered a haematologic urgency[1]
- If any of these tests are abnormal, nuclear scintigraphy should not be used to make the diagnosis of ATTR amyloidosis, and biopsy is recommended[1]

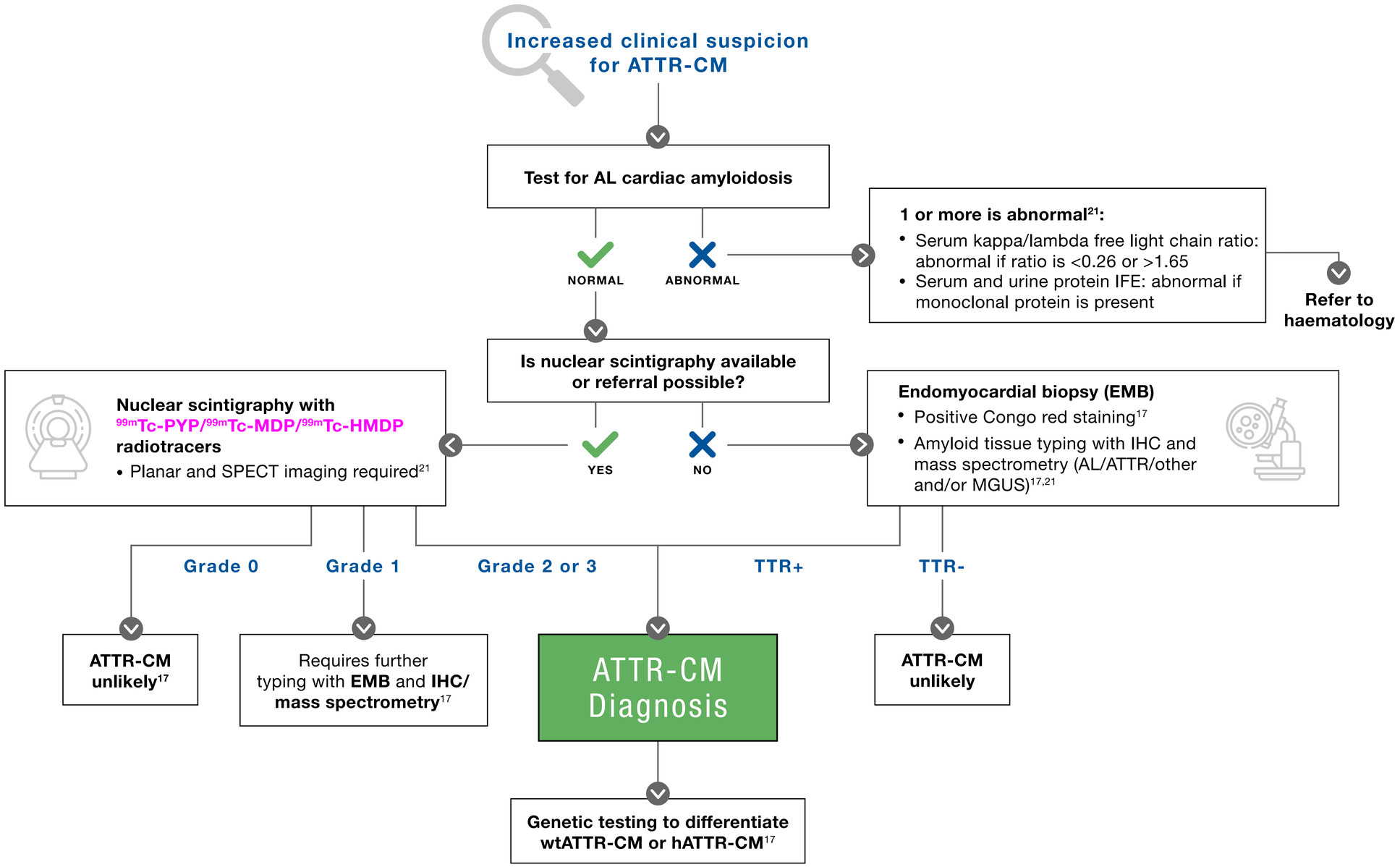
When cardiac amyloidosis is suspected, Grade 2 or 3 myocardial uptake (planar and SPECT), with concurrent testing to rule out AL, is diagnostic of ATTR-CM.[1]*†

*^{99m}Tc-PYP/^{99m}Tc-MDP/^{99m}Tc-HMDP uptake could be seen in other causes of myocardial injury, including pericarditis, myocardial infarction (regional uptake), and chemotherapy- or drug-associated myocardial toxicity.[17]

†Rule out AL: testing for presence of monoclonal protein via serum and urine immunofixation (IFE) and serum free light chain (SFLC) assay.[15]

Adapted from ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI Expert Consensus Recommendations.[1,2]

An ATTR-CM diagnostic flowchart



hATTR-CM, hereditary transthyretin amyloid cardiomyopathy; IHC, immunohistochemistry; MGUS, monoclonal gammopathy of undetermined significance; TTR, transthyretin; wtATTR-CM, wild-type transthyretin amyloid cardiomyopathy.

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Pfizer (Malaysia) Sdn Bhd 197801003134 (40131-T)
Level 10 & 11, Wisma Averis, Tower 2, Avenue 5,
Bangsar South, No. 8, Jalan Kerinchi,
59200 Kuala Lumpur.
Tel: +603 2281 6000 Fax: +603 2281 6388

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