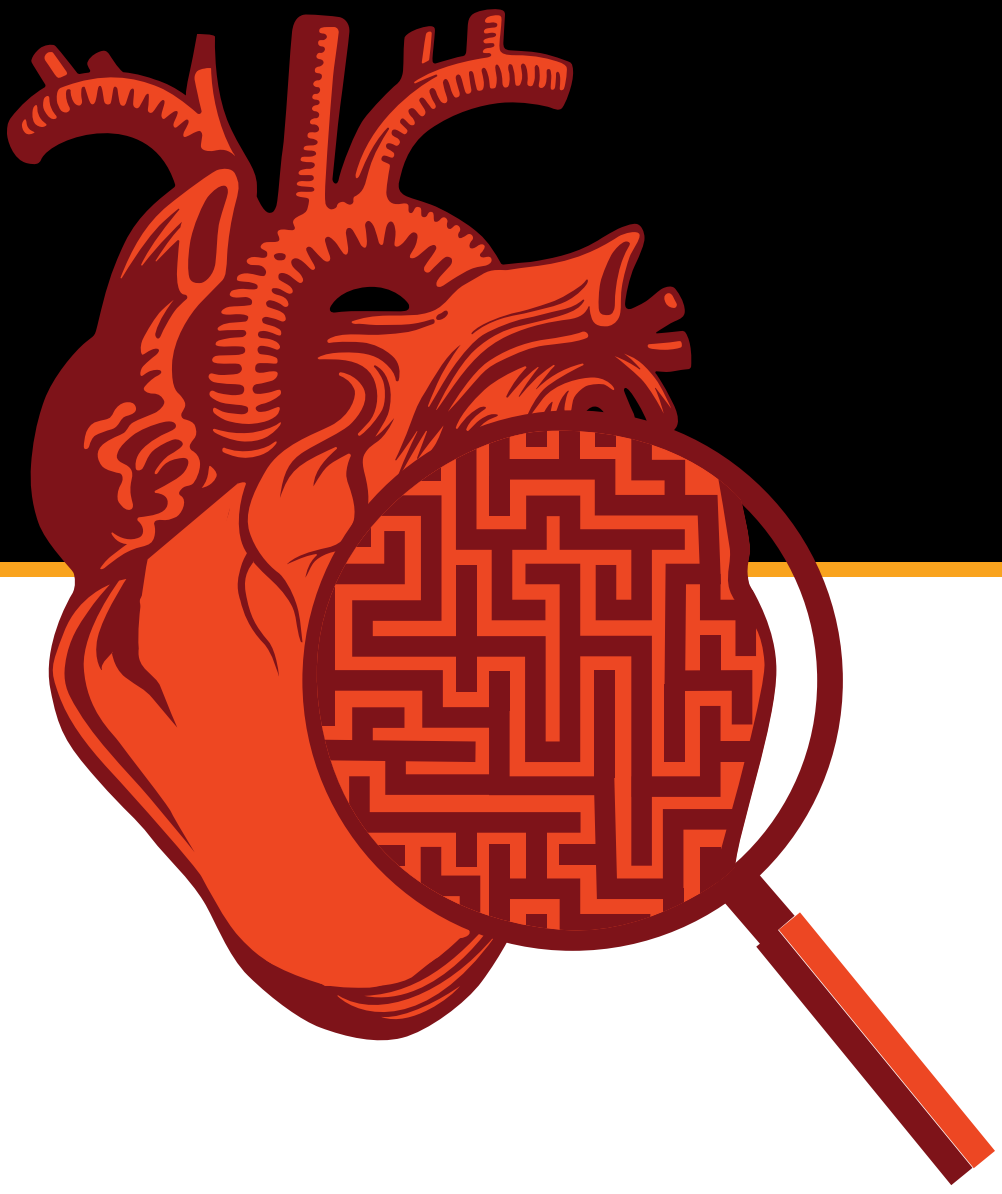
Transthyretin Amyloid Cardiomyopathy (ATTR-CM)

# Diagnostic Imaging of ATTR-CM With Nuclear Scintigraphy



ATTR-CM
SUSPECT & DETECT

Pfizer Rare Disease

# ATTR-CM and Its Clinical Clues

## A life-threatening, progressive, infiltrative, rare disease that can often be overlooked as a cause of heart failure[1,2]

Early diagnosis of ATTR-CM is critical, as prognosis worsens rapidly with continued amyloid deposition, subsequently advancing organ dysfunction, and significantly reducing quality of life.[1,3]

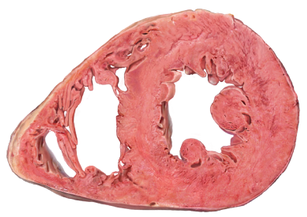
### Median Survival

Advanced-stage ATTR-CM in untreated patients is associated with serious cardiac complications and worse median survival[1,4]:

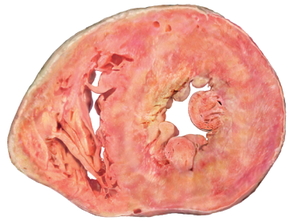
- Once diagnosed, untreated patients with ATTR-CM have a median survival of approximately 2 to 3.5 years[3]
- Early, accurate diagnosis of ATTR-CM may benefit patient care and lead to improved patient outcomes[1]

## 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, TO 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[5-7]

Intolerance to standard heart failure therapies, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and beta blockers[8]

Discordance between QRS voltage on electrocardiogram (ECG) and left ventricular (LV) wall thickness[9,10]

Echocardiography showing increased LV wall thickness[9]

Diagnosis of orthopaedic conditions, including carpal tunnel syndrome, lumbar spinal stenosis, biceps tendon rupture, and/or hip and knee arthroplasty[11-14]

Nervous system dysfunction, including polyneuropathy and autonomic dysfunction, including gastrointestinal complaints and/or unexplained weight loss[15]

*Notably those with a low-flow, low-gradient AS pattern.[6]

# Evidence for Nuclear Scintigraphy

## When ATTR-CM is suspected, diagnosis can be made noninvasively with nuclear scintigraphy and testing to rule out AL amyloidosis[16,17]

- Nuclear scintigraphy with $^{99m}$Tc-PYP*/$^{99m}$Tc-DPD/$^{99m}$Tc-HMDP provides a unique myocardial uptake pattern in amyloid[18]
- Studies comparing $^{99m}$Tc-PYP/$^{99m}$Tc-DPD/$^{99m}$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[18]
- Nuclear scintigraphy may identify ATTR deposits early in the course of disease[18]
- The mechanism for the differential uptake in ATTR vs AL cardiac amyloidosis is unknown, but it has been suggested that the preferential uptake by ATTR may be a result of higher calcium content[18]

## 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 on nuclear scintigraphy using technetium-labelled bone radiotracers pooling 529 patients with ATTR-CM estimated a sensitivity of 92.2% and a specificity of 95.4%
  - Diagnosis of ATTR-CM confirmed using visual analysis (visual grading score of ≥2 was considered positive for ATTR-CM)

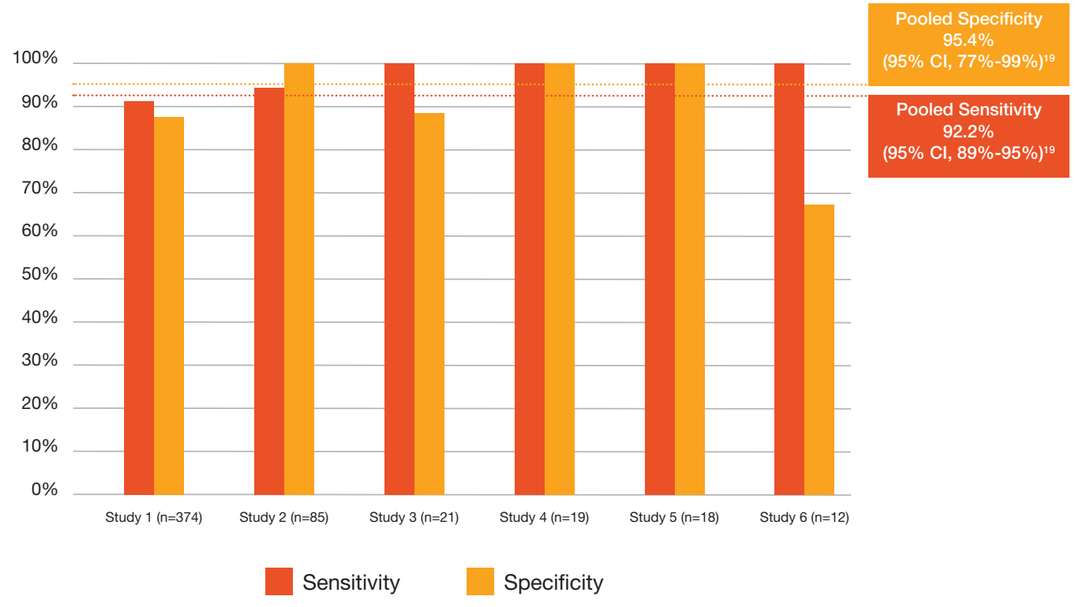
**Nuclear scintigraphy is a noninvasive, widely available diagnostic tool with high sensitivity and specificity for ATTR-CM when combined with testing to rule out AL amyloidosis[16,17]**

*$^{99m}$Tc-PYP is not FDA approved for the diagnosis of ATTR-CM. Please consult individual labelling for risks.

$^{99m}$Tc-DPD, $^{99m}$technetium-labelled 3,3-diphosphono-1,2-propanodicarboxylic acid; $^{99m}$Tc-HMDP, $^{99m}$technetium-labelled hydroxymethylene diphosphonate; $^{99m}$Tc-PYP, $^{99m}$technetium-labelled pyrophosphate; AL, immunoglobulin light chain amyloidosis.



## Diagnostic accuracy of ATTR-CM by nuclear scintigraphy with Tc-labelled radiotracers in a meta-analysis of 6 studies[19]




CI, confidence interval.

# Diagnosing ATTR-CM With $^{99m}$Tc-PYP/$^{99m}$Tc-DPD/$^{99m}$Tc-HMDP Imaging

## Multisocietal expert consensus recommendations for diagnosing ATTR-CM with nuclear scintigraphy[18]*

## IMAGING

### The role of $^{99m}$Tc-PYP/$^{99m}$Tc-DPD/$^{99m}$Tc-HMDP imaging in the diagnosis of ATTR-CM

- A variety of bone radiotracers have avidity for amyloid deposits[18]: $^{99m}$Tc-PYP/$^{99m}$Tc-DPD/$^{99m}$Tc-HMDP
- Images can be scanned early (1 hour) or late (3 hours)[18]
  - Interval between injection and scan[20]
- Both planar and single-photon emission computed tomography (SPECT) imaging should be reviewed and interpreted using visual and quantitative approaches irrespective of the timing of acquisition[18]

## INTERPRETATION

### 2-step interpretation of $^{99m}$Tc-PYP/$^{99m}$Tc-DPD/$^{99m}$Tc-HMDP* images to diagnose ATTR-CM[18]

*Note that the tracers 99mTc-HMDP and 99mTc-HDP are identical.

#### Step 1: Visual Interpretation

- Visual interpretation should include an evaluation of planar and SPECT images to confirm diffuse radiotracer uptake in the myocardium[18]
- SPECT imaging can be used to differentiate myocardial radiotracer uptake from residual blood pool activity, focal myocardial infarct, and overlapping bone (eg, from rib hot spots from fractures). Recommend repeating SPECT at 3 hours if excess blood pooling is noted at 1 hour[18]
- If myocardial tracer uptake is visually present on SPECT, proceed to step 2, semiquantitative grading[18]

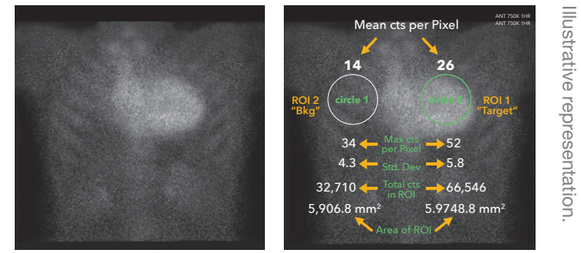
*Written by a writing group of experts in cardiovascular imaging and amyloidosis assembled by the American Society of Nuclear Cardiology and endorsed by 9 societies including the American College of Cardiology, American Heart Association, American Society of Echocardiography, European Association of Nuclear Medicine, Heart Failure Society of America, International Society of Amyloidosis, Society of Cardiovascular Magnetic Resonance, and Society of Nuclear Medicine and Molecular Imaging.



#### Step 2: Semiquantitative Grading

There are 2 approaches to performing semiquantitative grading[18]:

**1-hour approach: heart-to-contralateral lung (H/CL) ratio at 1 hour (validated for $^{99m}$Tc-PYP)[18,20]**

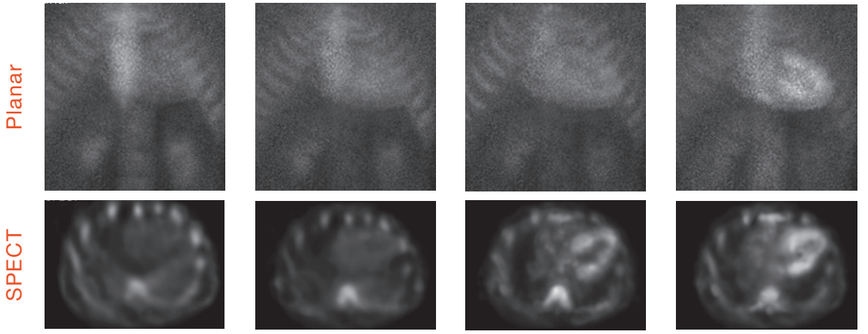



Illustrative representation.

Positive uptake | H/CL = 1.86

H/CL ratios of ≥1.5 at 1 hour can accurately identify ATTR cardiac amyloidosis if systemic AL is ruled out.[18]

**3-hour approach: visual comparison to bone (rib) uptake at 3 hours[18,20]**




Illustrative representation.

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

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.[18†]

**If clinical suspicion for cardiac amyloidosis remains high, despite a negative or inconclusive scintigraphy scan, consider EMB.[18]**

†Rule out AL: testing for presence of monoclonal protein via serum and urine immunofixation (IFE) and serum free light chain (SFLC) assay.[16]

$^{99m}$Tc-PYP, $^{99m}$technetium-labelled pyrophosphate.

## Interpretation Notes

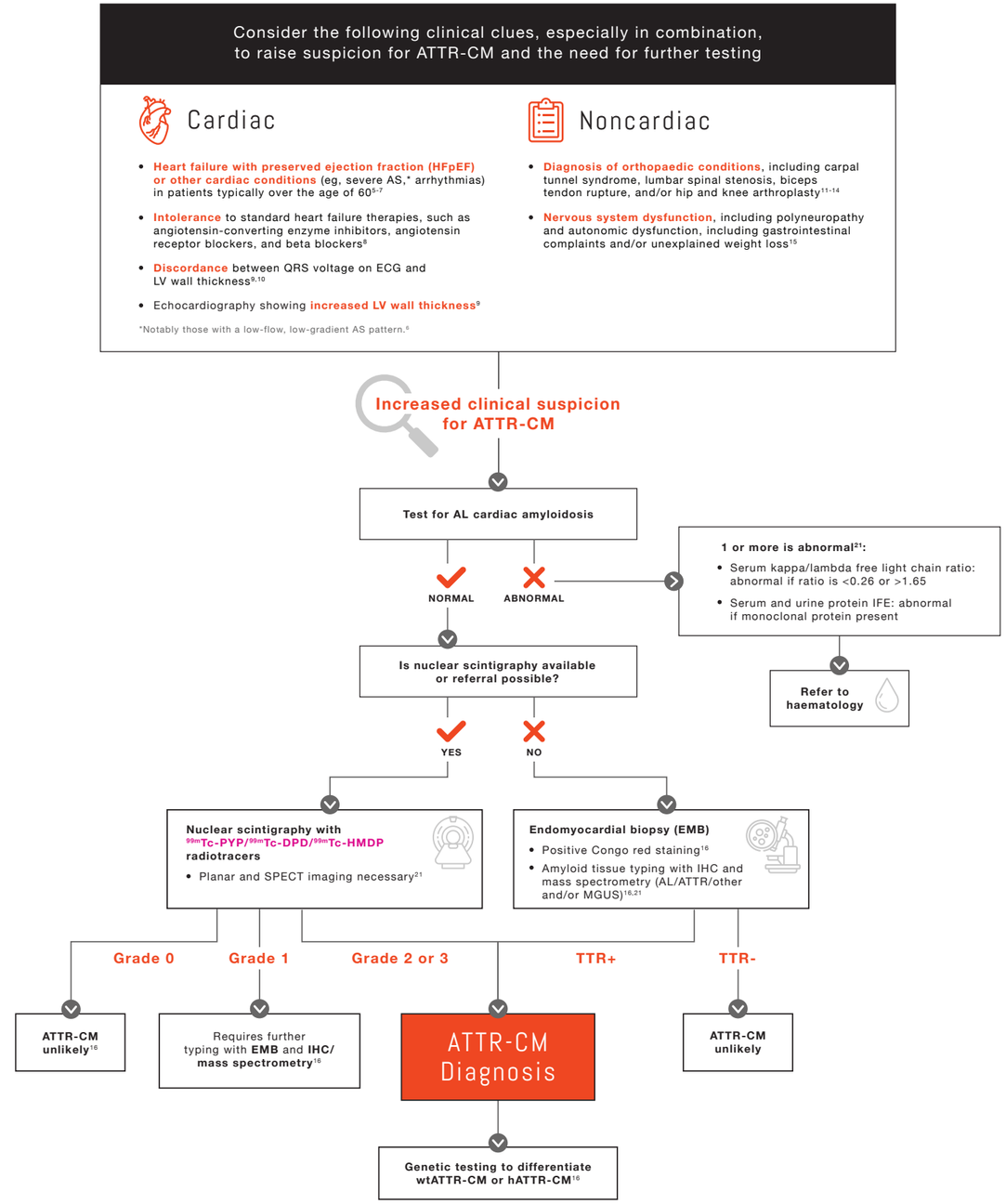
- SPECT imaging is necessary to differentiate myocardial uptake from blood pool or overlying bone uptake[18]
- Interpreting between focal vs diffuse radiotracer uptake[18]:
  - Diffuse uptake is typically consistent with cardiac amyloidosis
  - Focal uptake may represent early cardiac amyloidosis but has also been described in acute or subacute myocardial infarction
- The H/CL ratio may be falsely low in patients with a prior large remote myocardial infarction, as myocardial uptake of the tracer will be limited to noninfarcted zone[18]

## Ruling out AL

- AL is a main form of cardiac amyloidosis, which arises from overproduction and misfolding of monoclonal immunoglobulin light chains[18]
- Exclusion of a monoclonal process with serum and urine IFE and an SFLC assay in all patients with suspected amyloidosis is critical because because it is considered a haematologic urgency[18]
- If any of these tests are abnormal, nuclear scintigraphy should not be used to make the diagnosis of ATTR amyloidosis, and biopsy is recommended[18]



## 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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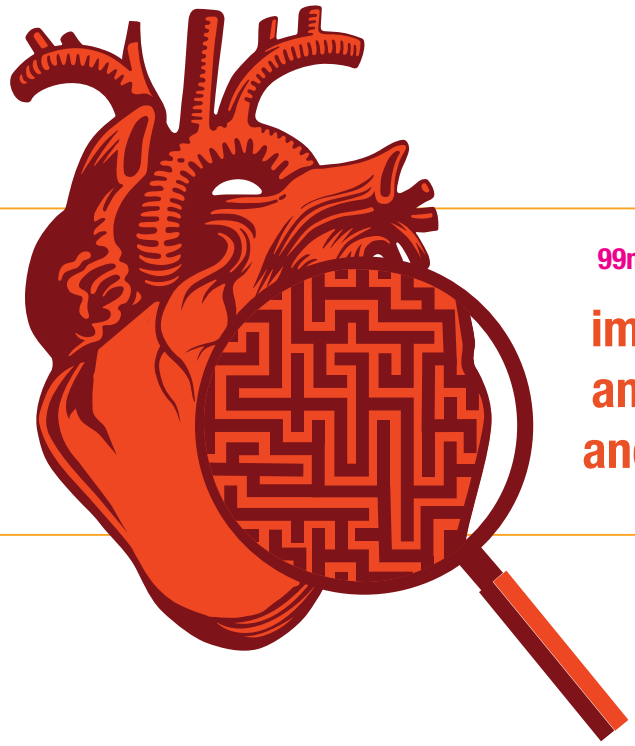
# ATTR-CM Diagnostic Imaging With Nuclear Scintigraphy



**$^{99m}$Tc-PYP/$^{99m}$Tc-DPD/$^{99m}$Tc-HMDP imaging can help lead to accurate and earlier diagnoses of ATTR-CM and drive appropriate intervention[1]**

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