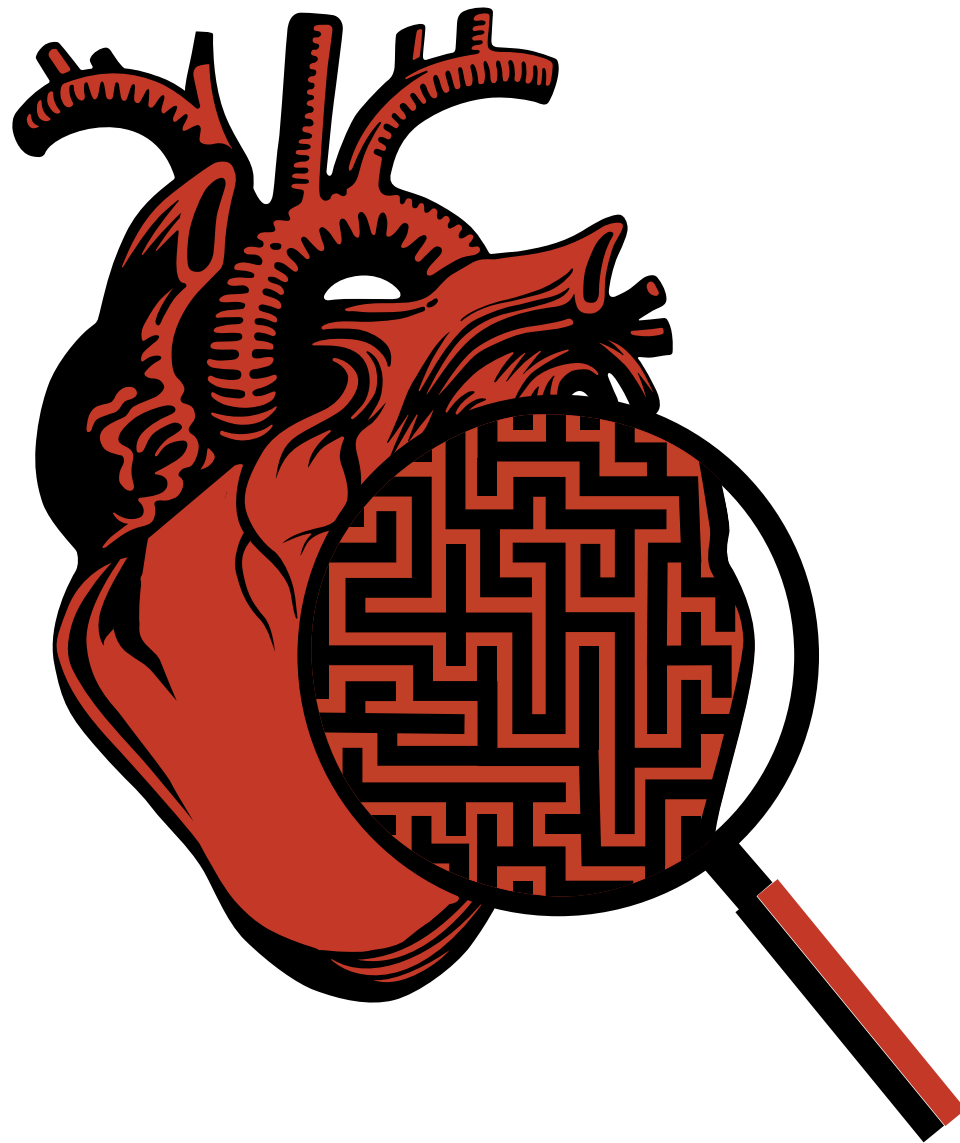


Transthyretin Amyloid Cardiomyopathy (ATTR-CM)

Diagnostic Imaging of ATTR-CM With Nuclear Scintigraphy



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}

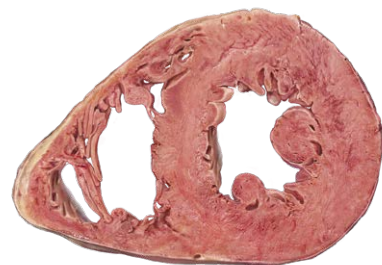
Median Survival

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 years³
- Early, accurate diagnosis of ATTR-CM may benefit patient care and lead to improved patient outcomes¹

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 60⁵⁻⁷



Intolerance to standard heart failure therapies, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and beta blockers⁸



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 arthroplasty¹¹⁻¹⁴



Nervous system dysfunction, including polyneuropathy and autonomic dysfunction, including gastrointestinal complaints and/or unexplained weight loss¹⁵

*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 amyloid¹⁸
- 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 absent¹⁸
- Nuclear scintigraphy may identify ATTR deposits early in the course of disease¹⁸
- 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 content¹⁸

Sensitivity and specificity of nuclear scintigraphy for ATTR-CM

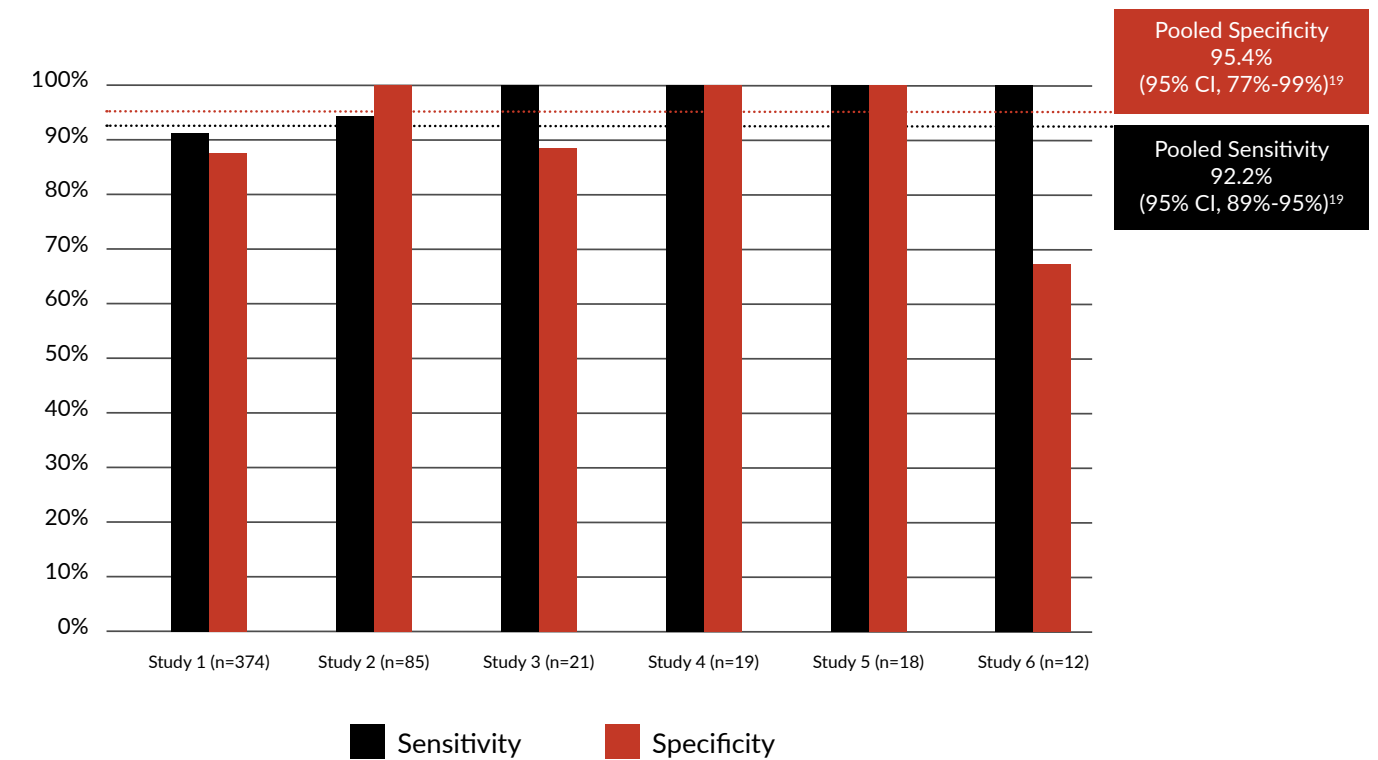
Multiple studies have demonstrated high sensitivity and specificity¹⁹

- 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 studies¹⁹



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 deposits¹⁸: ^{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 scan²⁰
- Planar as well as single-photon emission computed tomography (SPECT) imaging should be reviewed and interpreted using visual and quantitative approaches irrespective of the timing of acquisition¹⁸

Interpretation

2-step interpretation of ^{99m}Tc-PYP/^{99m}Tc-DPD/^{99m}Tc-HMDP images to diagnose ATTR-CM¹⁸

Step 1: Visual Interpretation

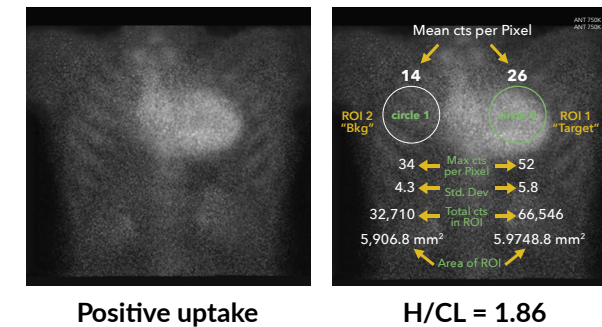
- Visual interpretation should include an evaluation of planar and SPECT images to confirm diffuse radiotracer uptake in the myocardium¹⁸
- SPECT imaging can be used to differentiate myocardial radiotracer uptake from residual blood pool activity, focal myocardial infarct, and overlapping bone (eg, from rib hot spots from fractures). Recommend repeating SPECT at 3 hours if excess blood pooling is noted at 1 hour¹⁸
- If myocardial tracer uptake is visually present on SPECT, proceed to step 2, semiquantitative grading¹⁸

*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 grading¹⁸:

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

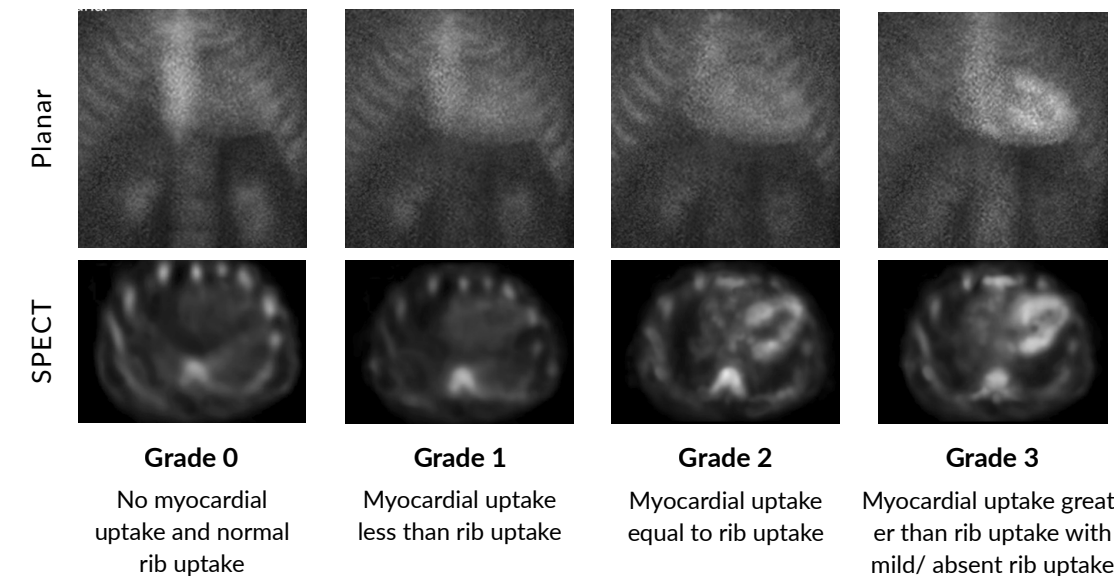


Illustrative representation.



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.



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 uptake¹⁸



- Interpreting between focal vs diffuse radiotracer uptake¹⁸:
 - 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

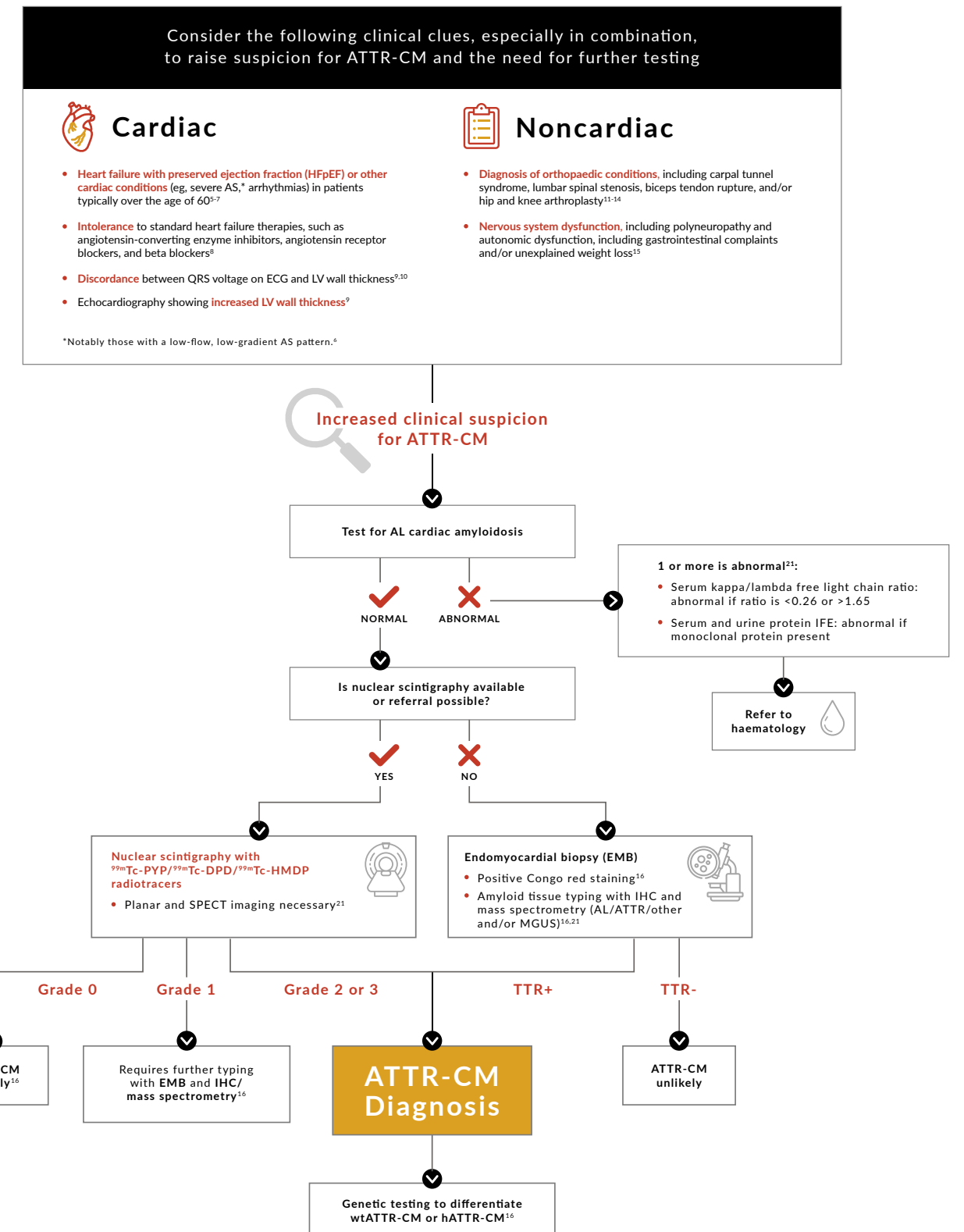


- The H/CL ratio may be falsely low in patients with a prior large remote myocardial infarction, as myocardial uptake of the tracer will be limited to noninfarcted zone¹⁸

Ruling out AL

- AL is a main form of cardiac amyloidosis, which arises from overproduction and misfolding of monoclonal immunoglobulin light chains¹⁸
- 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 urgency¹⁸
- If any of these tests are abnormal, nuclear scintigraphy should not be used to make the diagnosis of ATTR amyloidosis, and biopsy is recommended¹⁸

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.

EURO-LEARN CARDIAC AMYLOIDOSIS SCINTIGRAPHY

AN INITIATIVE BY ESMIT

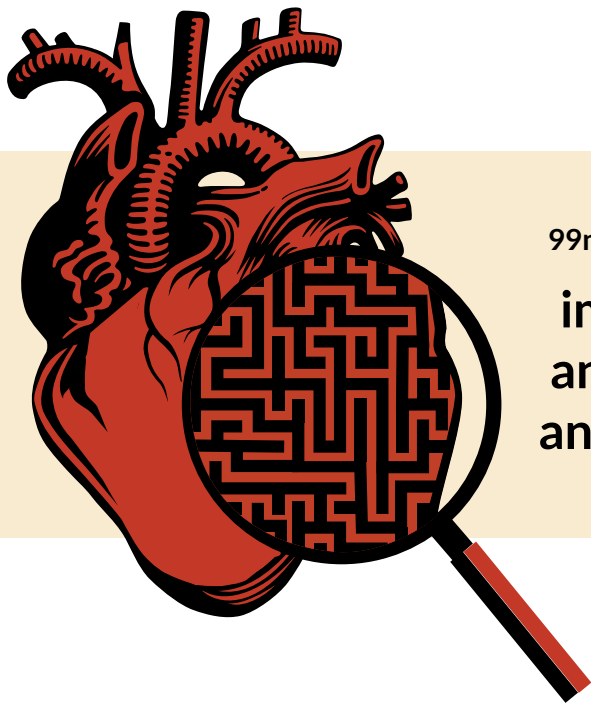
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ATTR-CM Diagnostic Imaging With Nuclear Scintigraphy



^{99m}Tc -PYP/ ^{99m}Tc -DPD/ ^{99m}Tc -HMDP imaging can help lead to accurate and earlier diagnoses of ATTR-CM and drive appropriate intervention¹

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