Imaging Cardiac Amyloidosis with 99mTc-PYP

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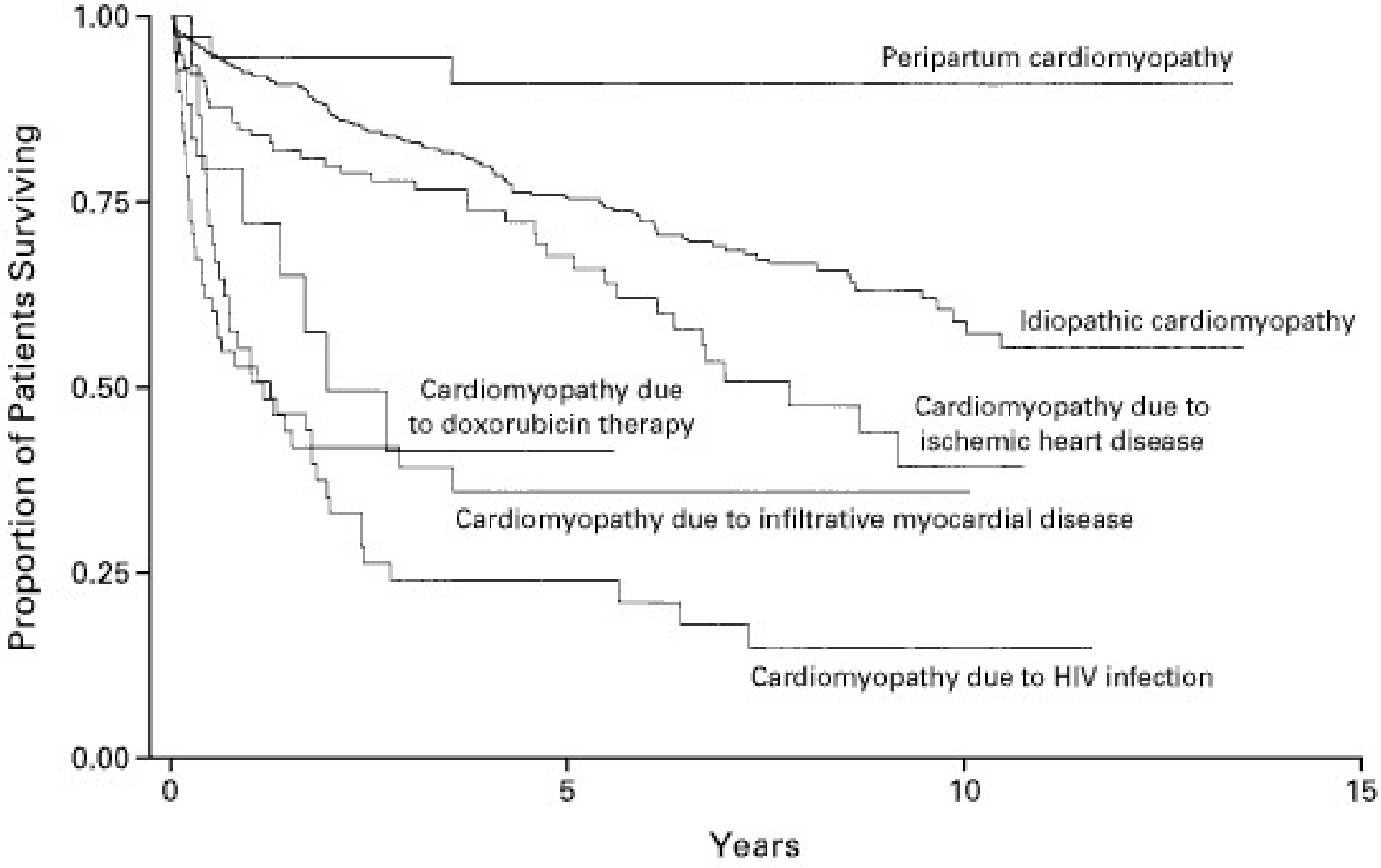
IONETIX

Disclosures

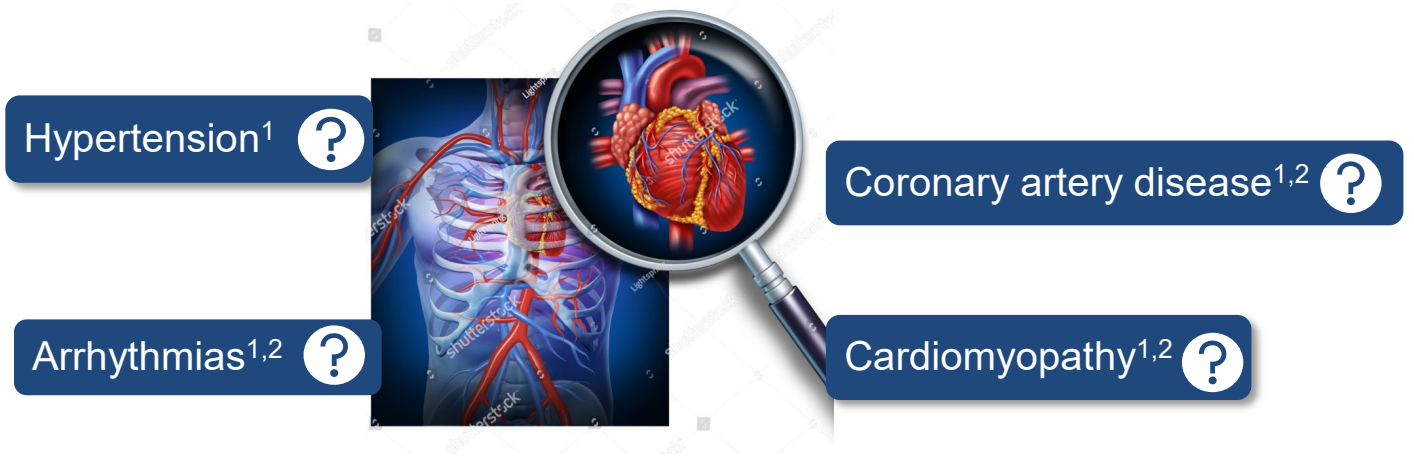
- Ionetix Corporation - employee

Learning Objectives

- Provide information about cardiac amyloidosis
- Review use of Tc-99m PYP imaging for cardiac amyloidosis
- Describe preparation and administration techniques of Tc-99m PYP
- Describe imaging acquisition parameters
- Describe image processing


Proportion of Patients Surviving
1.00
0.75
0.50
0.25
0.00
0
5
10
15
Years
Peripartum cardiomyopathy
Idiopathic cardiomyopathy
Cardiomyopathy due to ischemic heart disease
Cardiomyopathy due to doxorubicin therapy
Cardiomyopathy due to infiltrative myocardial disease
Cardiomyopathy due to HIV infection

Cardiac Amyloid is One of Several, Varied Causes of Heart Failure



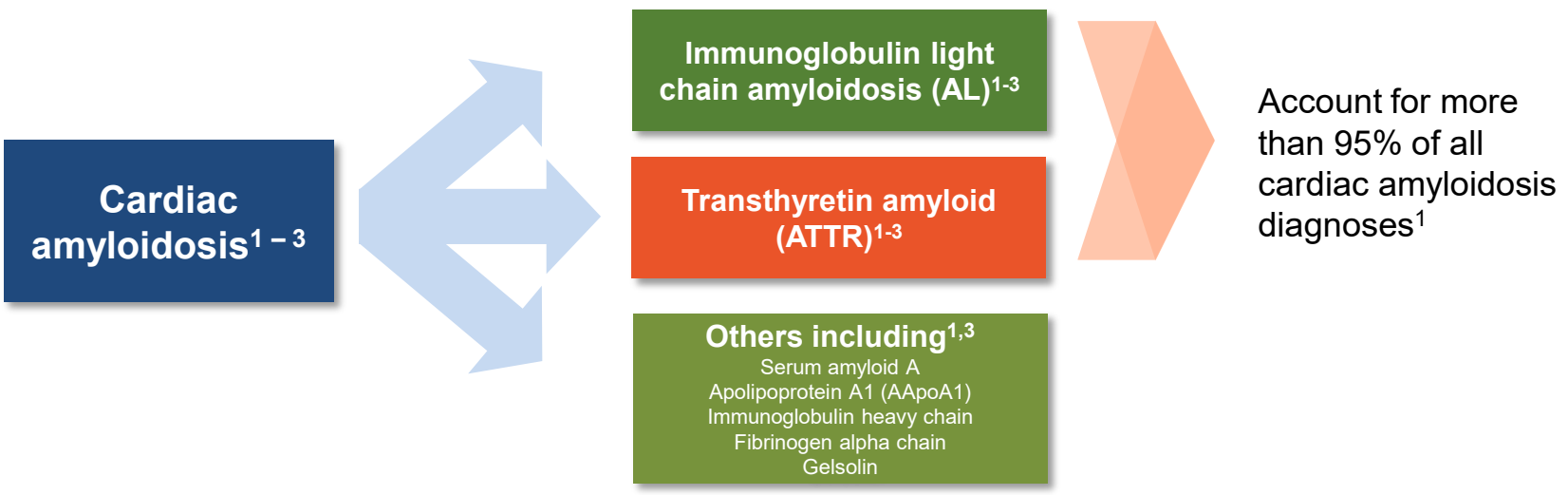
Cardiac amyloidosis is a life-threatening, infiltrative cardiomyopathy that commonly is a cause of heart failure, characterized by extracellular deposition of misfolded protein which forms amyloid fibrils that deposit in the heart[3–6]

1. Mayo Clinic: heart failure. http://www.mayoclinic.org/diseases-conditions/heart-failure/symptoms-causes/syc-20373142. Accessed November 19, 2018. 2. Ponikowski P, et al. *Eur Heart J.* 2016;37(27):2129-2200. 3. Siddiqi OK, Ruberg FL. *Trends Cardiovasc Med*. 2018;28(1):10-21. 4. Halwani O, Delgado DH. *Expert Rev Cardiovasc Ther*. 2010;8(7):1007-1113. 5. Rapezzi C, et al. *Heart Fail Rev*. 2015;20(2):117-124. 6. Maurer MS, et al. *Circulation*. 2017;135(14):1357-1377.

Cardiac Amyloidosis is Underrecognized

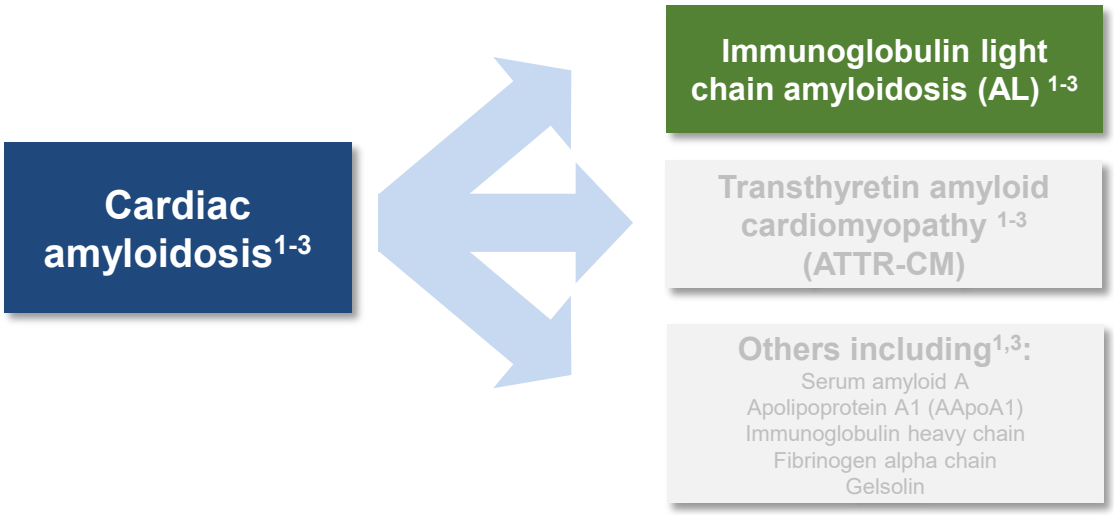
1. Rapezzi C, et al. *Heart Fail Rev*. 2015;20(2):117-124.

Main Types of Cardiac Amyloidosis



1. Donnelly J, Hanna M. *Cleve Clin J Med.* 2017;84(12 suppl 3):12-26. 2. Siddiqi OK, et al. *Trends Cardiovasc Med.* 2018;28:10–21 3. Kholová I, Niessen HW. *J Clin Pathol.* 2005;58(2):125-133.

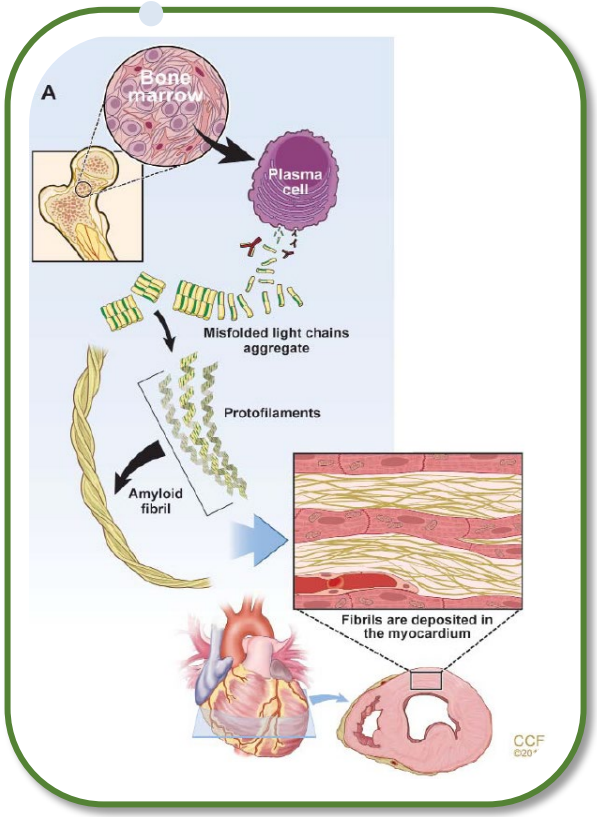
AL Amyloidosis



1. Donnelly J, Hanna M. *Cleve Clin J Med.* 2017;84(12 suppl 3):12-26. 2. Siddiqi OK, et al. *Trends Cardiovasc Med.* 2018;28:10–21 3. Kholová I, Niessen HW. *J Clin Pathol.* 2005;58(2):125-133.

AL Amyloidosis

- **AL amyloidosis is a plasma cell dyscrasia**[1,2]
  - Monoclonal plasma cells overproduce immunoglobulin light-chain fragments, which misfold to form amyloid fibrils
- ~3,000 new cases per year in the US[1,3]
- Presents in those aged >50 years[2]



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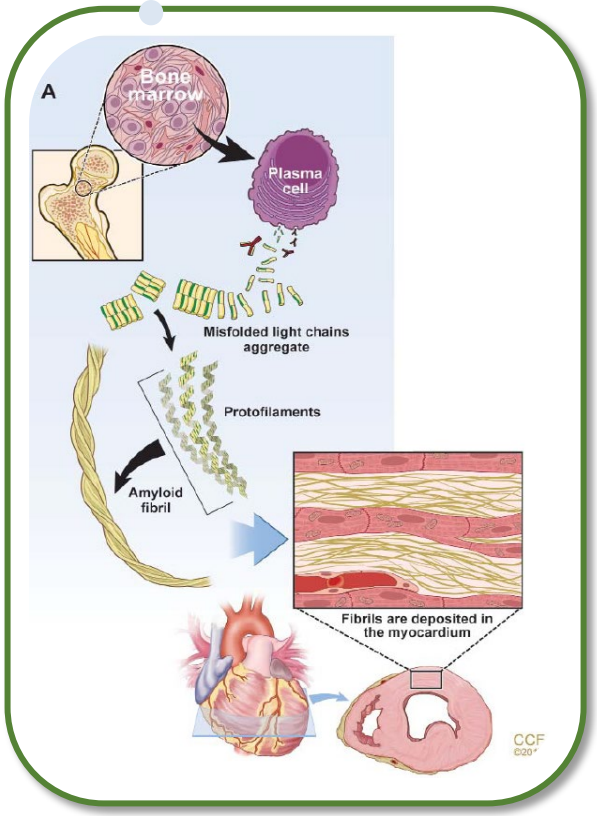
1. Donnelly J, Hanna M. *Cleve Clin J Med.* 2017;84(12 Suppl 3):12–26. 2. Dubrey SW, et al. *Heart.* 2011;97:75–84. 3. Milani P, et al. *Mediterr J Hematol Infect Dis.* 2018;10:e2018022. 4. Maurer MS, et al. *Circulation* 2017;135:1357–1377. 5. Siddiqi OK, et al. *Trends Cardiovasc Med.* 2018;28:10–21.

AL Amyloidosis

- **AL amyloidosis is a plasma cell dyscrasia**[1,2]
  - Monoclonal plasma cells overproduce

Median survival of untreated patients with AL amyloidosis who present with heart failure is <6 months[1]

- ~3,000 new cases per year in the US[1,3]
- Presents in those aged >50 years[2]



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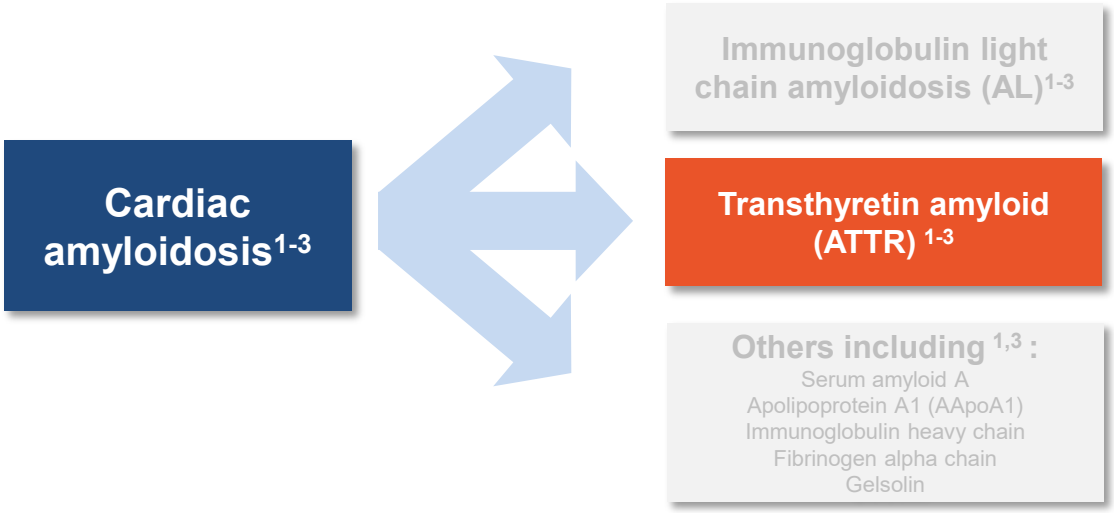
1. Donnelly J, Hanna M. *Cleve Clin J Med.* 2017;84(12 Suppl 3):12–26. 2. Dubrey SW, et al. *Heart.* 2011;97:75–84. 3. Milani P, et al. *Mediterr J Hematol Infect Dis.* 2018;10:e2018022. 4. Maurer MS, et al. *Circulation* 2017;135:1357–1377. 5. Siddiqi OK, et al. *Trends Cardiovasc Med.* 2018;28:10–21.

Transthyretin Amyloid Cardiomyopathy ATTR-CM



1. Donnelly J, Hanna M. *Cleve Clin J Med.* 2017;84(12 suppl 3):12-26. 2. Siddiqi OK, et al. *Trends Cardiovasc Med.* 2018;28:10–21 3. Kholová I, Niessen HW. *J Clin Pathol.* 2005;58(2):125-133.

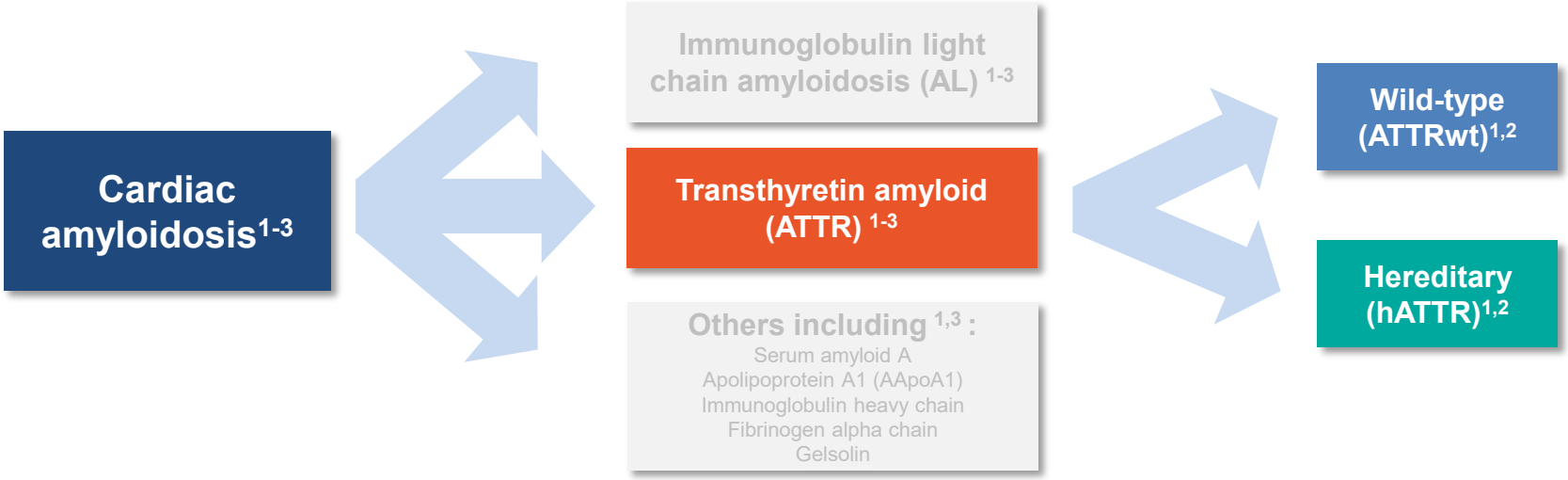
Mechanism of ATTR-CM

Figure adapted with permission from Nativi-Nicolau et al.[4]

ATTR-CM: Life-threatening, underrecognized, and underdiagnosed[1–4]

1. Maurer MS, et al. *Circulation*. 2017;135(14):1357-1377. **2.** Donnelly J, Hanna M. *Cleve Clin J Med.* 2017;84(12 suppl 3):12-26. 3. Ando Y, et al. *Orphanet J Rare Dis*. 2013;8:31. 4. Nativi-Nicolau J, et al. *Curr Opin Cardiol*. 2018;33(5):571-579.

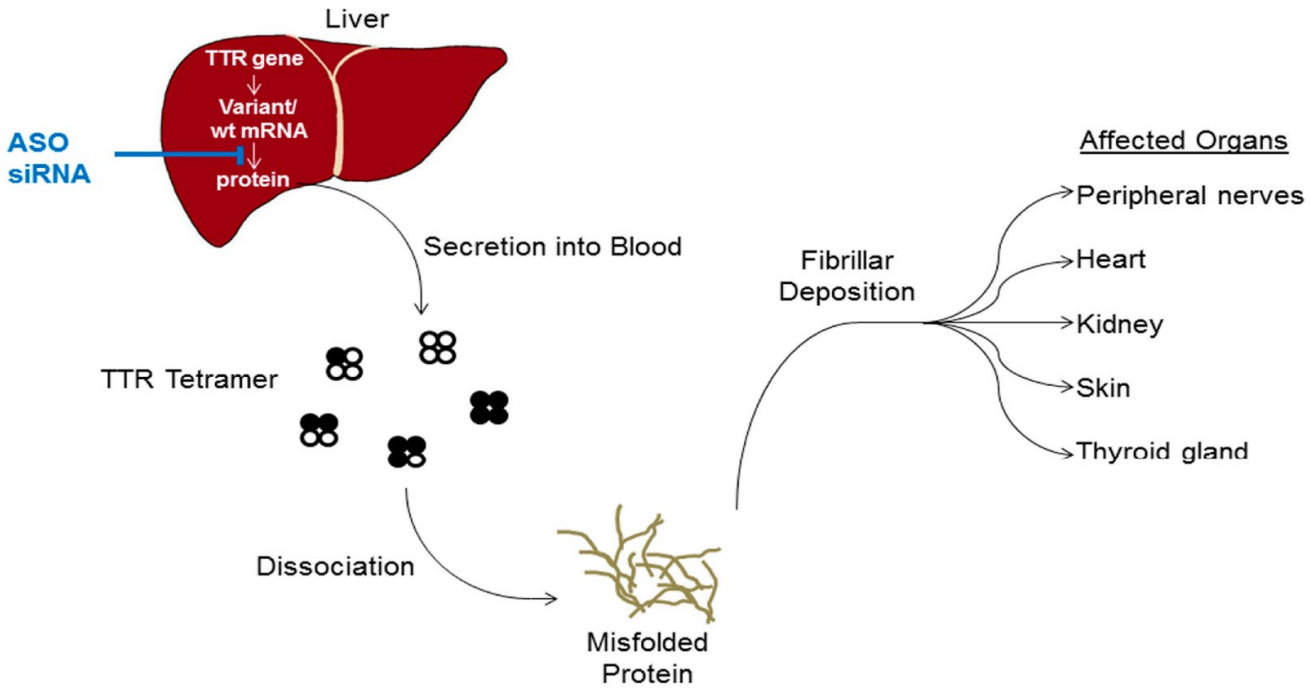
ATTR-CM Subtypes



1. Donnelly JP, et al. *Cleve Clin J Med*. 2017;84(12 Suppl 3):12–26. 2. Siddiqi OK, et al. *Trends Cardiovasc Med*. 2018;28:10–21. 3. Kholova I, Niessen HWM. *J Clin Pathol.* 2005;58(2):125–133.

TTR – Familial or Hereditary Cardiac Amyloidosis

TTR - familial or hereditary genetic defects increase the chance of this amyloid disease



Deposition of Amyloid Fibrils in the Myocardium

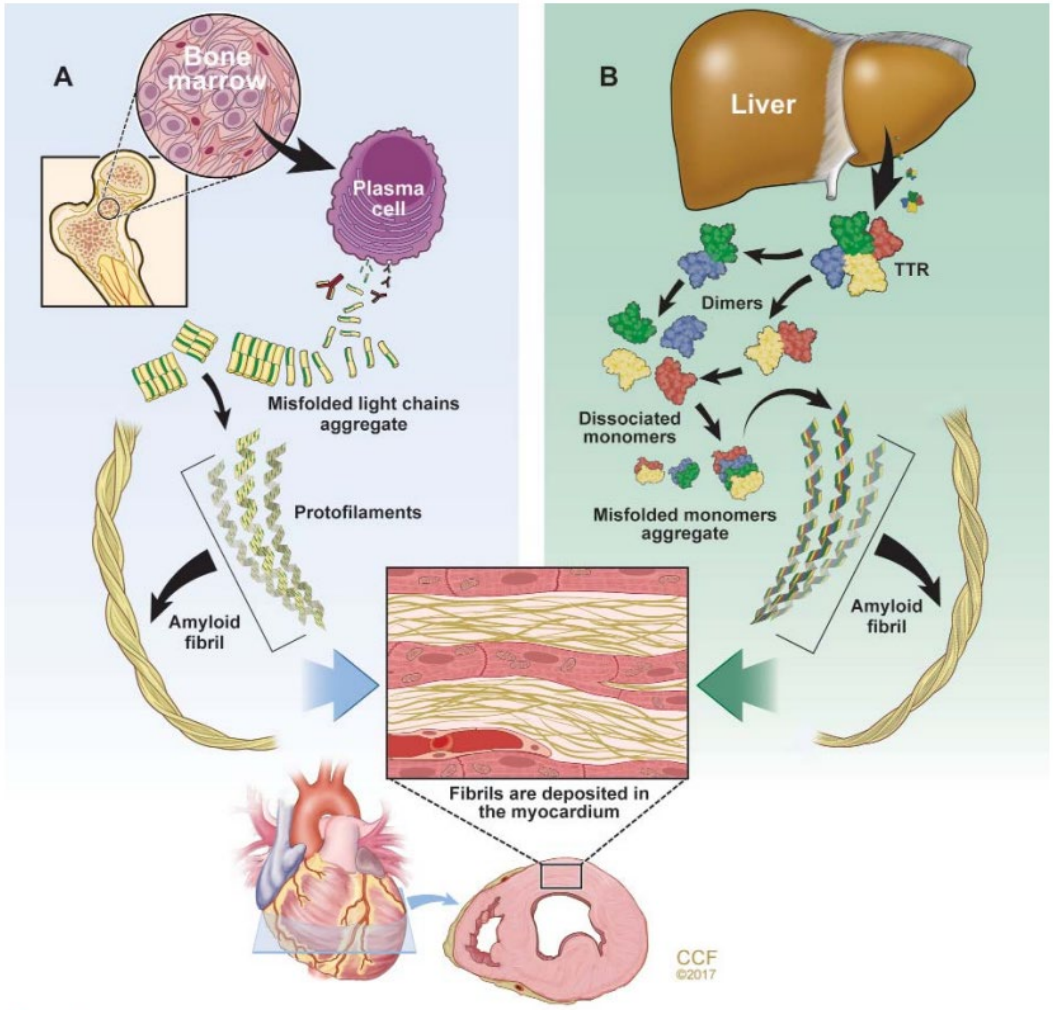


Figure 1. The 2 main types of amyloidosis that affect the heart. (A) Immunoglobulin light chain amyloidosis (AL) results from aberrant plasma cell production of monoclonal light chains that misfold. (B) Transthyretin amyloidosis (ATTR) results from transthyretin (TTR) produced by the liver that dissociates into monomers and misfolds. The misfolded proteins aggregate to form oligomers, protofilaments, and mature amyloid fibrils that deposit extracellulary in the interstitial space of the myocardium.

Types of Cardiac Amyloidosis

Features	AL Amyloid	mATTR	wtATTR
Precursor Protein	Light chain	Mutant TTR	TTR
Average Age (Range)	55 (30-75)	50 (30-70)	75 (60-100)
Gender (% Male)	60%	80%	95%
Cardiac Involvement (%)	30%	Variable	All
Fat Pad Biopsy	50-80%	20%	<20%
Primary Referral Route	Hematology Cardiology Nephrology	Neurology Cardiology	Cardiology

Cardiac Amyloidosis

Cardiac amyloid effects on the heart:

- Stiff myocardium
- Loss of myocardial contractility
- Heart rhythm abnormality
- Decrease in blood flow

HEART FAILURE SYMPTOMS

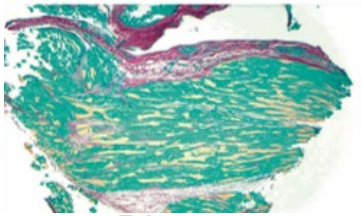
Symptoms:

- Shortness of breath
- Irregular heart beats
- Feet and ankle edema
- Weakness, fatigue, and nausea

Testing Options

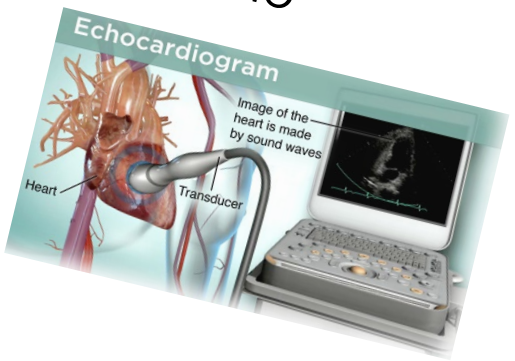
EKG

Bloodwork



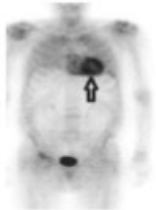
Biopsy

ECHO

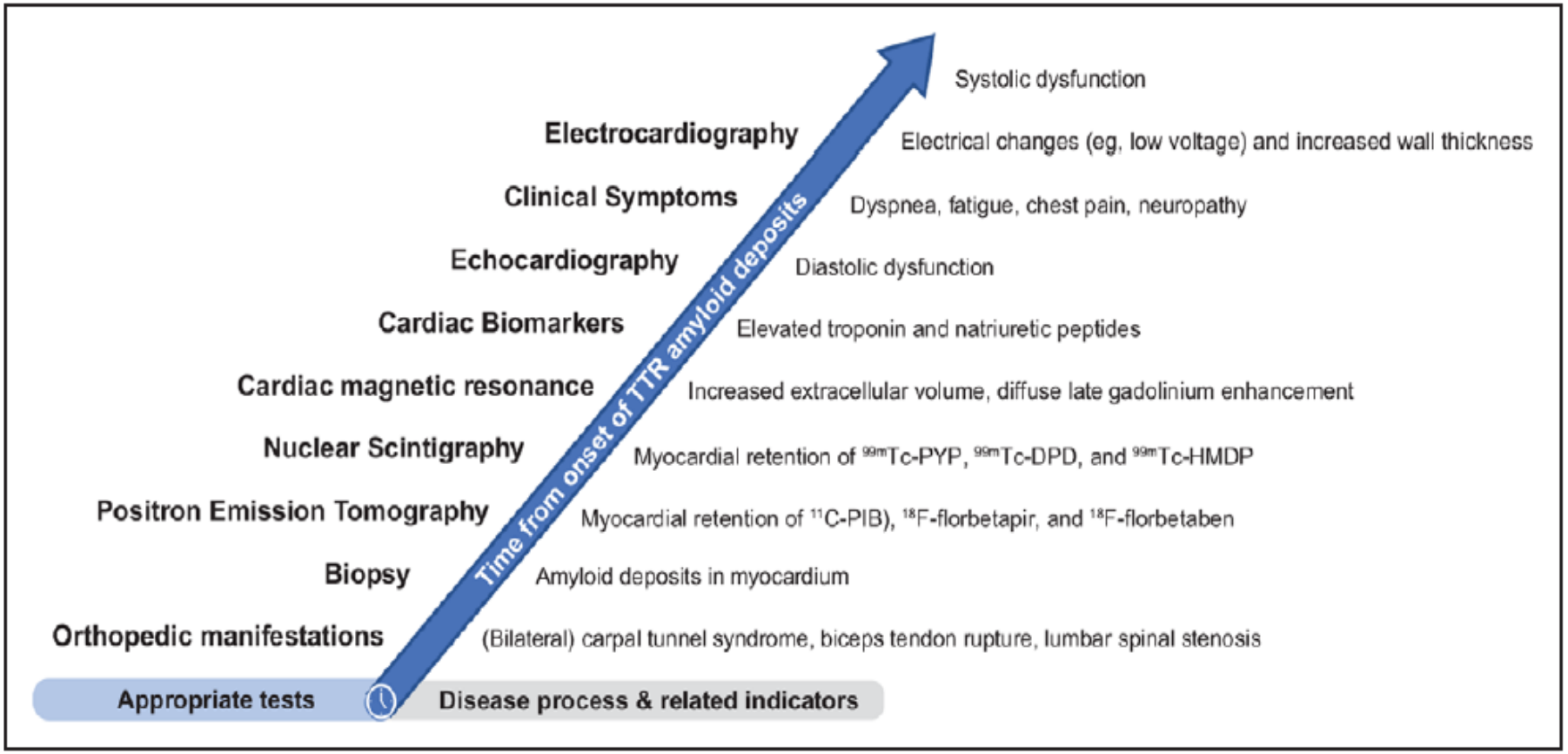


MRI

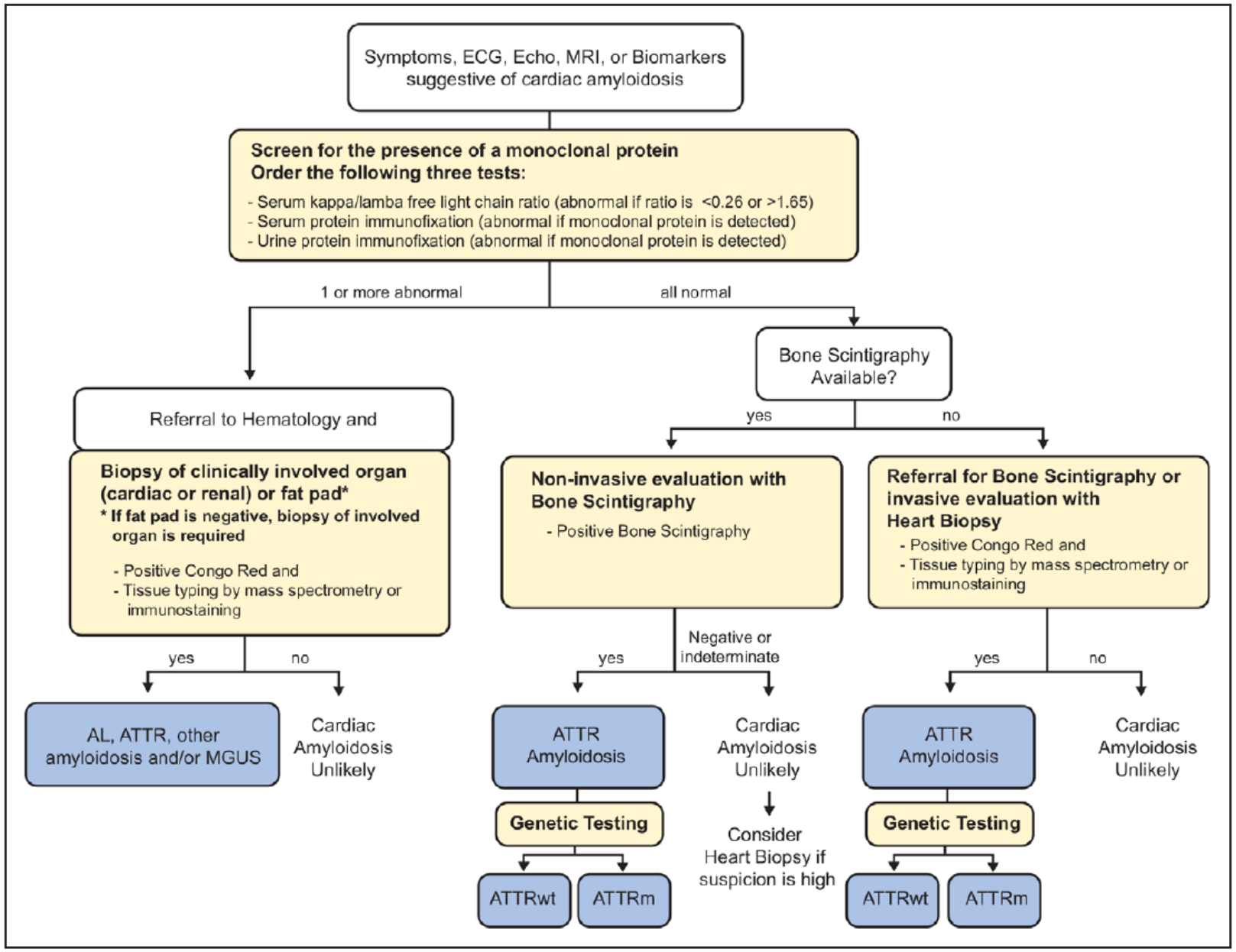
Tc-99m PYP



Clinical Timeline of Disease

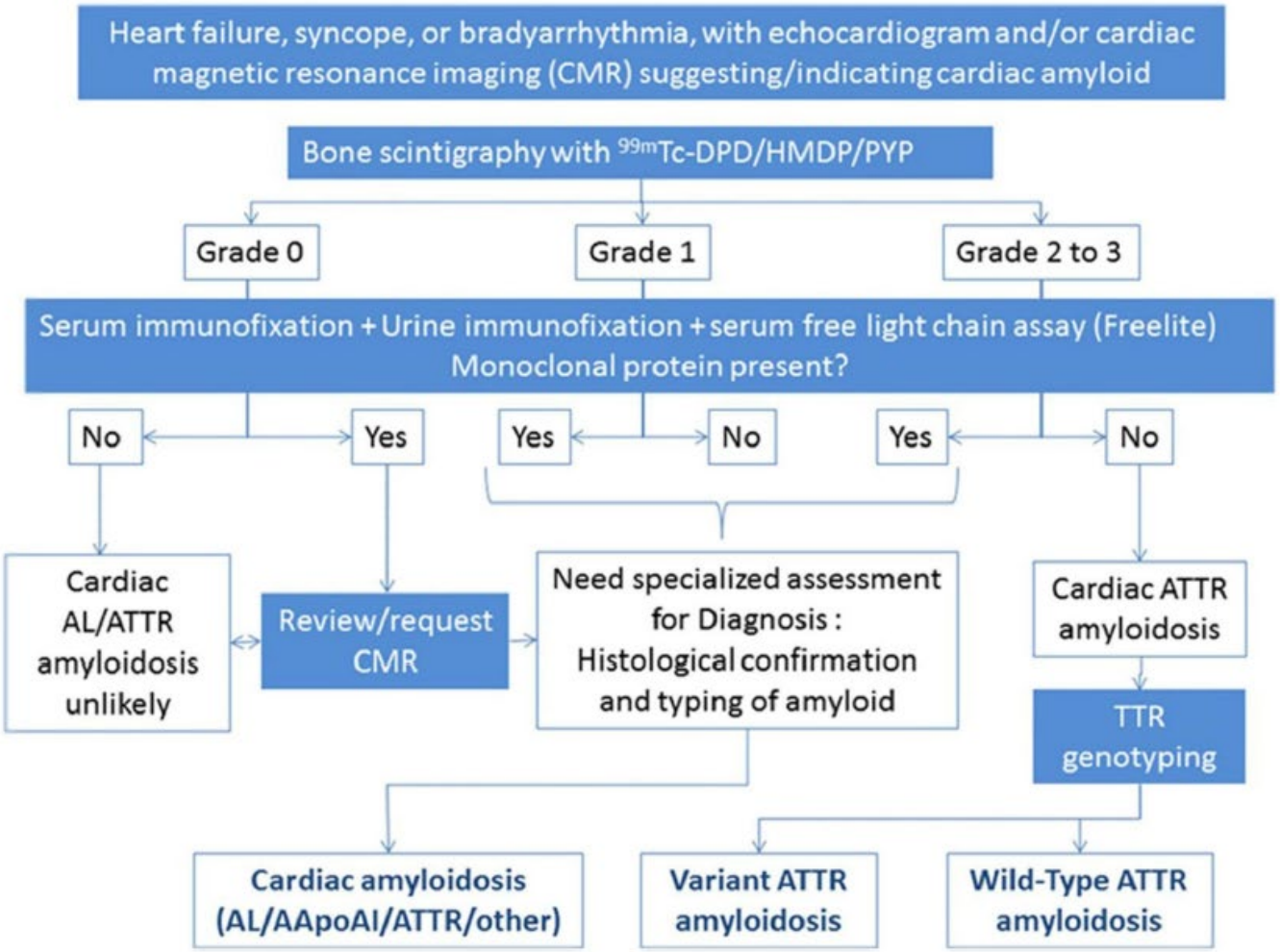


Maurer MS, *et al*. Expert Consensus Recommendations for the Suspicion and Diagnosis of Tranthyretin Cardiac Amyloidosis. *Circ: Heart Failure* 2019; 12: e006075



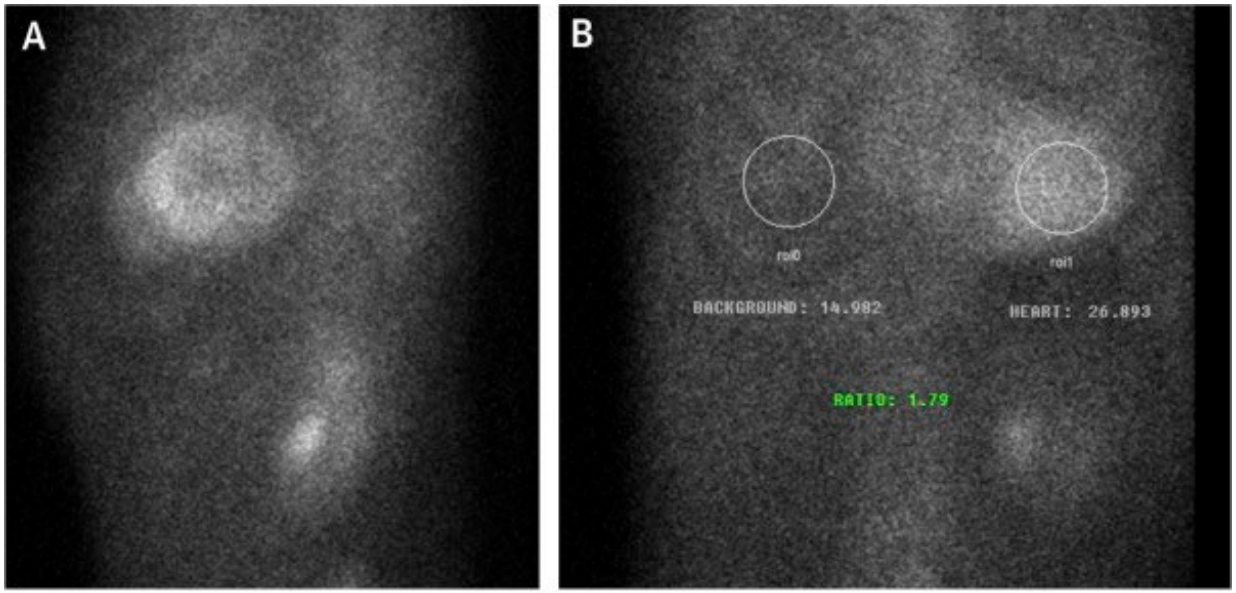
Maurer MS, *et al*. Expert Consensus Recommendations for the Suspicion and Diagnosis of Tranthyretin Cardiac Amyloidosis. *Circ: Heart Failure* 2019; 12: e006075

Nuclear Imaging Pathway



Dorbala S, *et al*. Expert Consensus Recommendations for Multimodality Imaging in Cardiac Amyloidosis. *JNC* 2019.

99mTcPYP Scintigraphy or PYP Scan



- 99mTcPYP, a radiotracer used in bone scans, was initially used in cardiology to quantify myocardial infarction due to its ability to localize calcium
- Potential utility came in 1982 when diffuse myocardial 99mTcPYP uptake on cardiac radionucleotide imaging was noted in 10 patients with tissue-proven amyloidosis
- Significant uptake in ATTR and no to mild uptake in AL: a specificity and positive predictive value of 100% in the absence of monoclonal gamopathy
- Not only confirms the diagnosis of CA but differentiates ATTR-CA

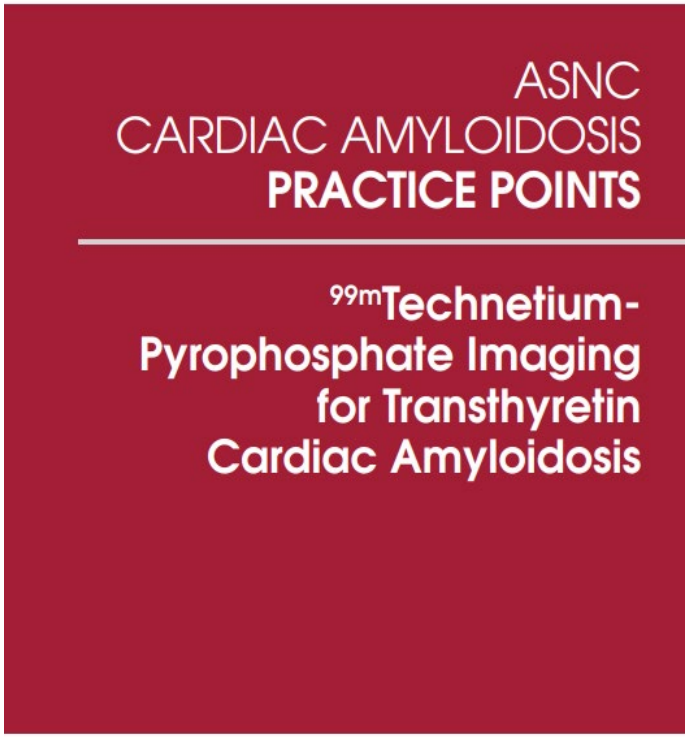
99mTc-PYP Kit Preparation

- Let vial of PYP come to room temperature for 5 minutes
- Draw 100 mCi 99mTc and QS to 4ml with saline to give final concentration = 100mCi/4ml
- Add to PYP reaction vial
- Invert vial several times to shake and reconstitute the 99mTc and PYP
- After 99mTc and PYP are mixed let vial rest for 5 minutes

Recommended Imaging Procedures
ASNC Practice Points

Imaging procedures	Parameters
Preparation	No specific preparation. No fasting required.
Scan	Rest scan
Dose of ^{99m}Tc-PYP	10-20 mCi intravenously
Time between injection and acquisition	Recommended: 1-hour SPECT and planar; Optional: 3-hour SPECT or planar
Imaging parameters	
Field of view	Recommended: Cardiac or chest; Optional: Wholebody planar
Image type	Recommended: Cardiac or chest SPECT and planar imaging
Position	Supine
Energy window	140 keV, 15-20%
Collimators	Low energy, high resolution
Matrix	64 X 64 minimum
Pixel size	3.5 – 6.5 mm
Planar imaging specific parameters	
Number of views*	Anterior, Lateral, and Left Anterior Oblique
Detector configuration	90 degrees
Image duration (count based)	750,000 counts
Magnification	1.46
SPECT imaging specific parameters	
Angular range	360 degrees
Detector configuration	180 degrees
ECG gating	Off; Nongated imaging
Number of views/ detector	40
Time per stop	20 seconds
Magnification	1.0

*Anterior and lateral views can be obtained at the same time using a 90 degree detector configuration; lateral planar views or SPECT imaging may help separate sternal from myocardial uptake.



American Society of Nuclear Cardiology (ASNC). ASNC practice points: 99mTechnetium-pyrophosphate imaging for transthyretin cardiac amyloidosis. Available at: https://www.asnc.org/Files/Practice%20Resources/Practice%20Points/ASNC%20Practice%20Point-99mTechnetiumPyrophosphateImaging2016.pdf. © 2019 American Society of Nuclear Cardiology.

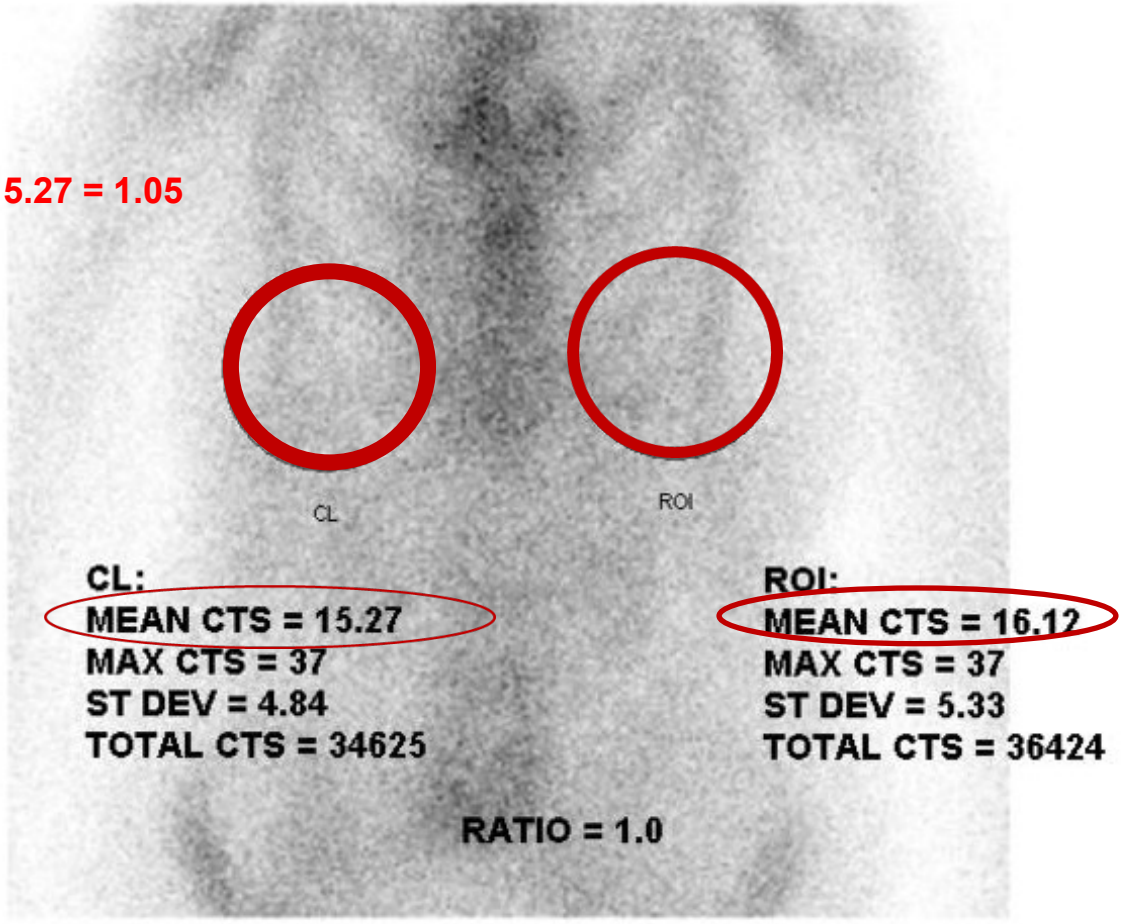
Imaging Procedure

- Cardiac or chest SPECT and planar images are obtained one hour after injection of 99mTc-PYP
- If persistent blood pool activity is noted on one hour images (e.g., renal failure), delayed images may be obtained at 3 hours
- Planar imaging is useful for visual interpretation and quantification of the degree of myocardial uptake
- SPECT imaging is useful:
  - to avoid overlap of bone uptake
  - distinguish blood pool activity from myocardial activity
  - assess the distribution of myocardial 99mTc-PYP uptake in individuals with positive planar scans
  - identify 99mTc-PYP uptake in the interventricular septum (commonly involved in amyloidosis)
  - quantify the degree of myocardial uptake by comparison to rib uptake.
- Whole body planar imaging may be helpful to identify uptake of 99mTcPYP in the shoulder and hip girdles (a specific sign of systemic ATTR amyloidosis)
- The value of 99mTc-PYP imaging with the newer “cardiac only” SPECT cameras is currently being evaluated – validate with camera manufacturer

American Society of Nuclear Cardiology (ASNC). ASNC practice points: 99mTechnetium-pyrophosphate imaging for transthyretin cardiac amyloidosis. Available at: https://www.asnc.org/Files/Practice%20Resources/Practice%20Points/ASNC%20Practice%20Point-99mTechnetiumPyrophosphateImaging2016.pdf. © 2019 American Society of Nuclear Cardiology.

Quantitative Evaluation

ROI=16.12/15.27 = 1.05



ROI Processing – Planar Image

Circular ROI over the heart (ROI)
Circular ROI right side of the chest: Contralateral chest ROI (CL)

Avoid placing either ROI over the sternum, ribs, and liver!
Record: Mean counts, Max counts, St Dev counts, Total counts for ROI and CL

$$\textbf{RATIO} = \frac{\text{Mean counts of the ROI (cardiac)}}{\text{Mean counts of the CL (contralateral)}}$$

RATIO >1.5 suggestive of cardiac amyloidosis

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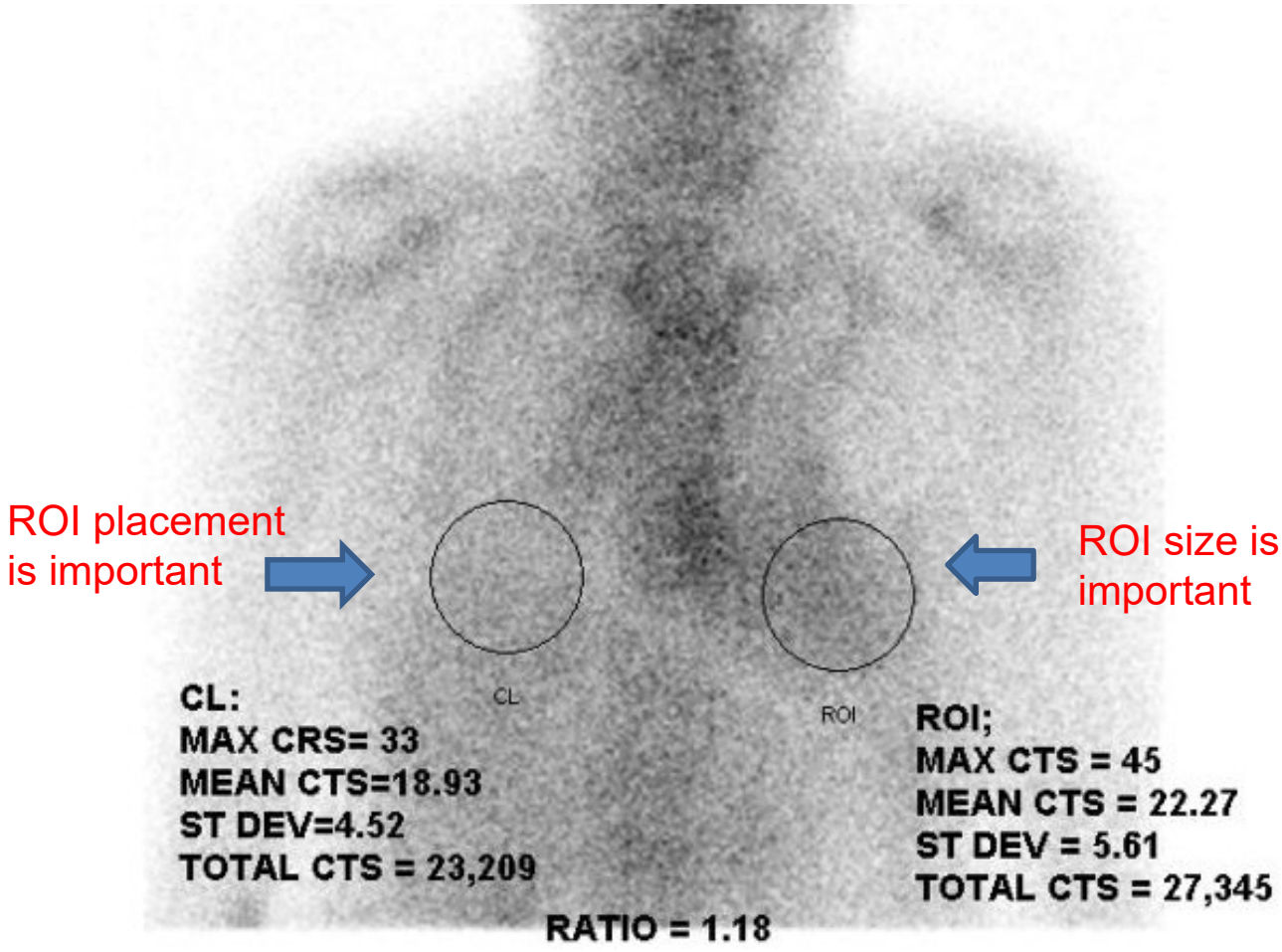
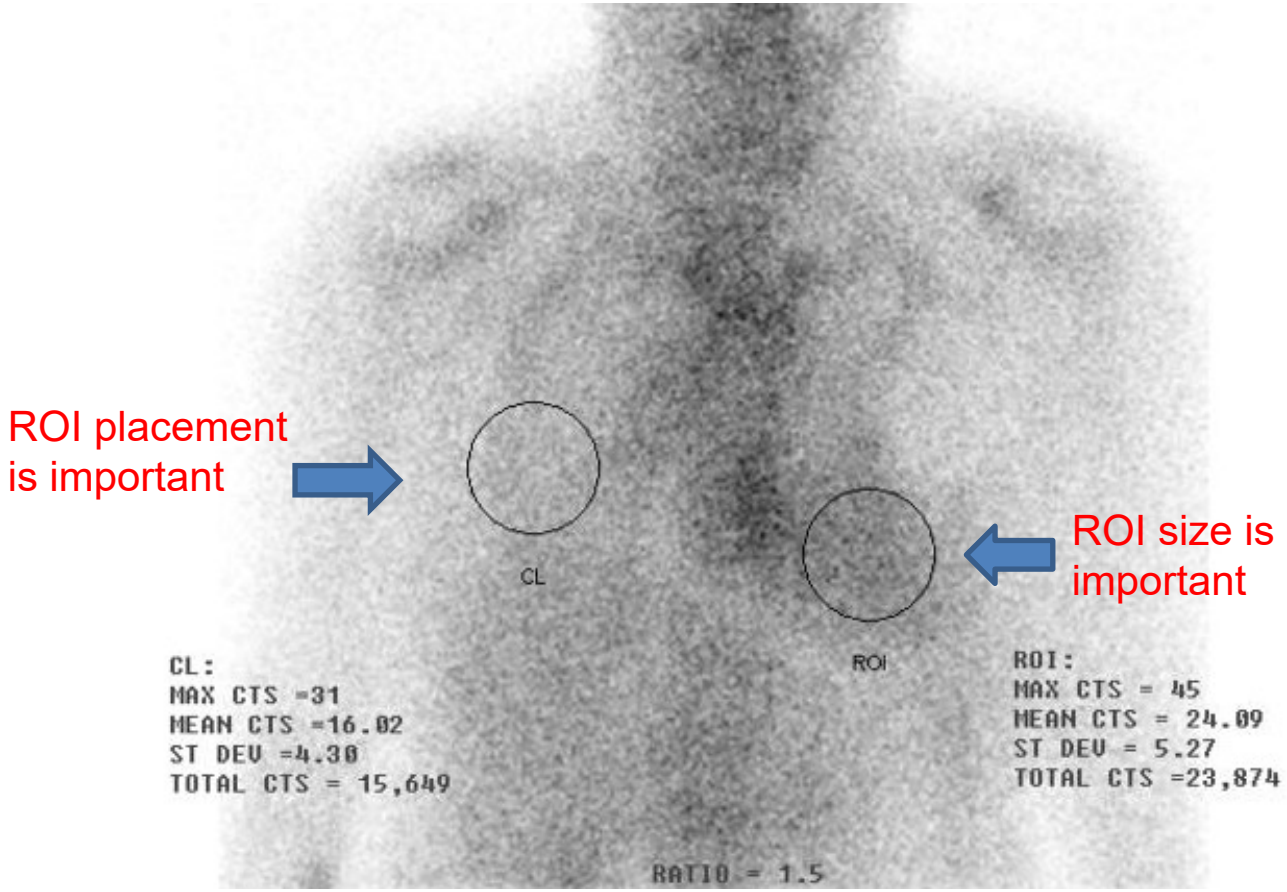
Size and Placement of ROI



Reprocessed ROI



Processing – SPECT Images

- SPECT images can be processed according to the patient's heart-to-contralateral lung (H/CL) ratio
  - For patients that have a **ratio of <1.5** process as a
  - bone/chest SPECT
  - If the patient's **ratio is ≥1.5** process as a MPI study

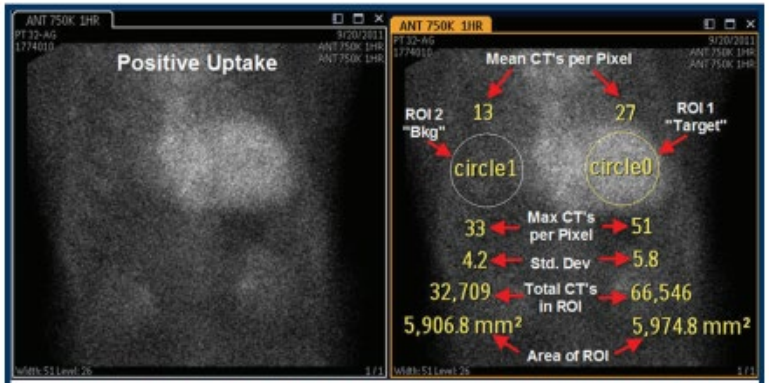
American Society of Nuclear Cardiology (ASNC). ASNC practice points: 99mTechnetium-pyrophosphate imaging for transthyretin cardiac amyloidosis. Available at: https://www.asnc.org/Files/Practice%20Resources/Practice%20Points/ASNC%20Practice%20Point-99mTechnetiumPyrophosphateImaging2016.pdf. © 2019 American Society of Nuclear Cardiology.

Semi-Quantitative Visual Grading

Table 2. Semi-quantitative Visual Grading of Myocardial ^{99m}Tc-PYP Uptake by Comparison to Bone (rib) Uptake

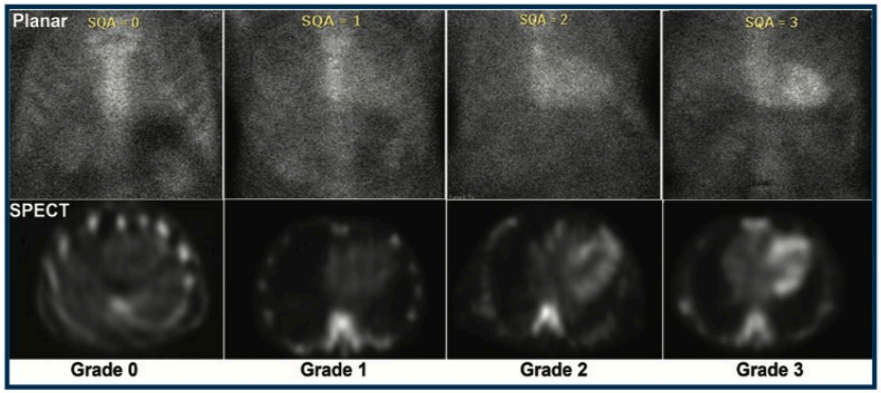
Grade	Myocardial ^{99m}Tc-PYP Uptake
Grade 0	no uptake and normal rib uptake
Grade 1	uptake less than rib uptake
Grade 2	uptake equal to rib uptake
Grade 3	uptake greater than rib uptake with mild/absent rib uptake

Figure 1. Quantitation of Cardiac ^{99m}Tc-PYP Uptake Using Heart-to-Contralateral Lung (H/CL) Ratio



Biopsy proven ATTR cardiac amyloidosis with H/CL = 2.08

Figure 2. Grading ^{99m}Tc-PYP Uptake on Planar and SPECT Images



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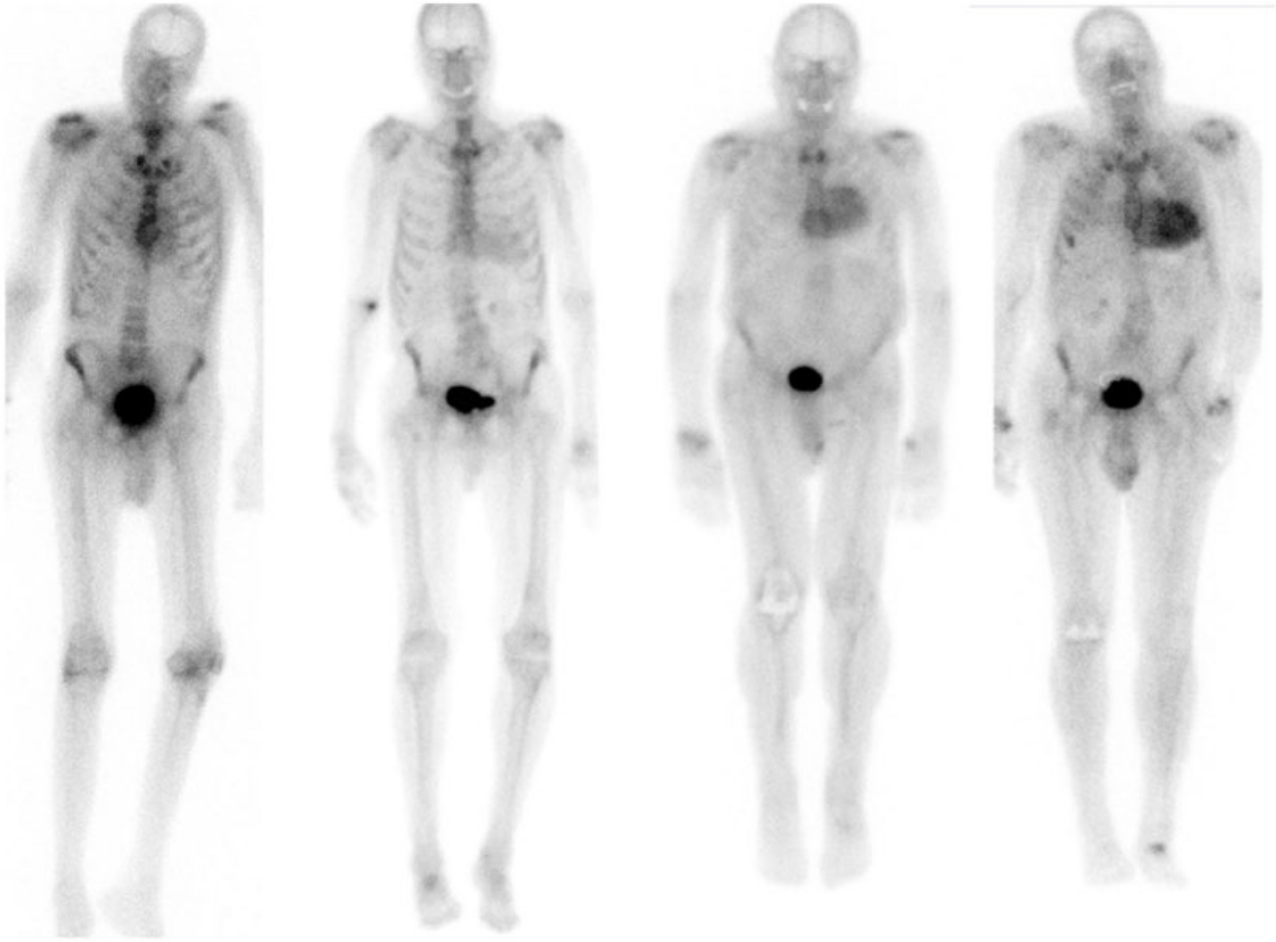
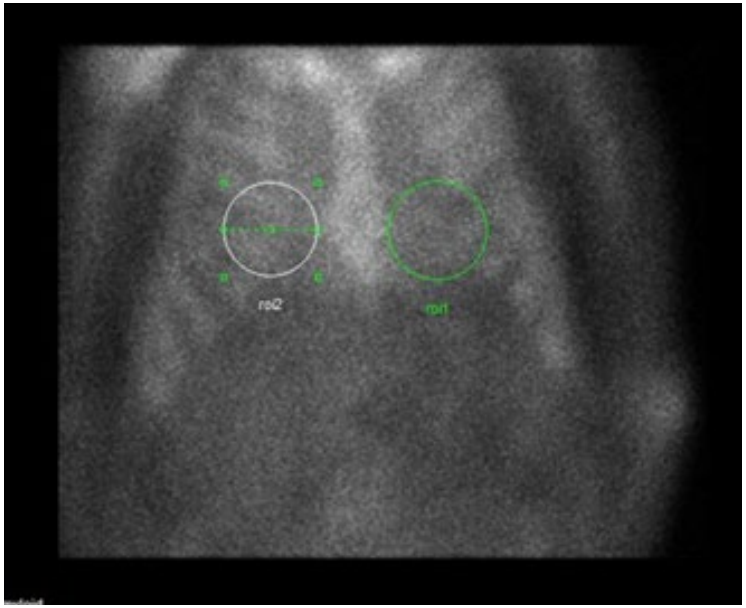
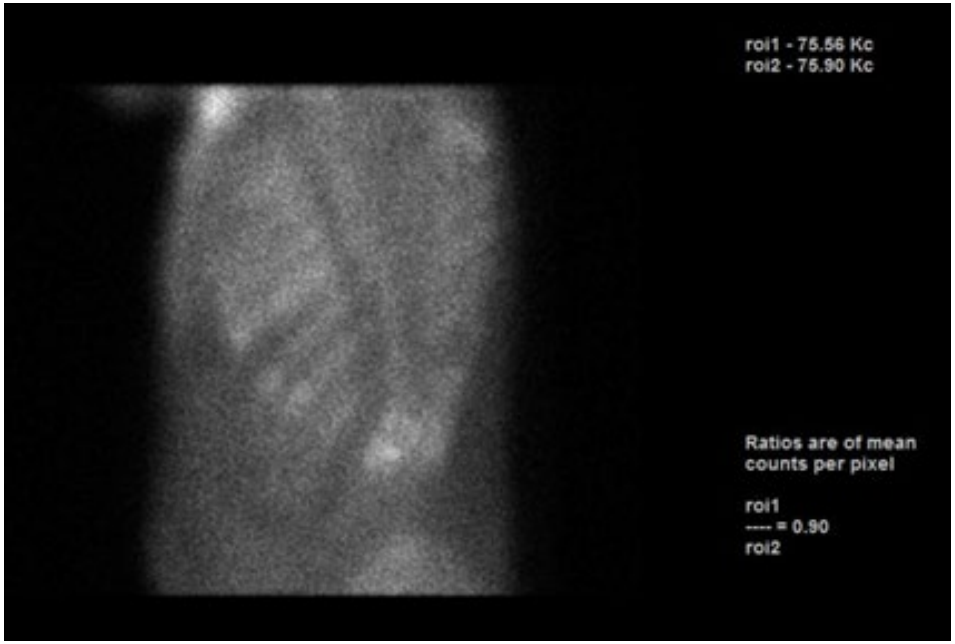
Whole Body Imaging



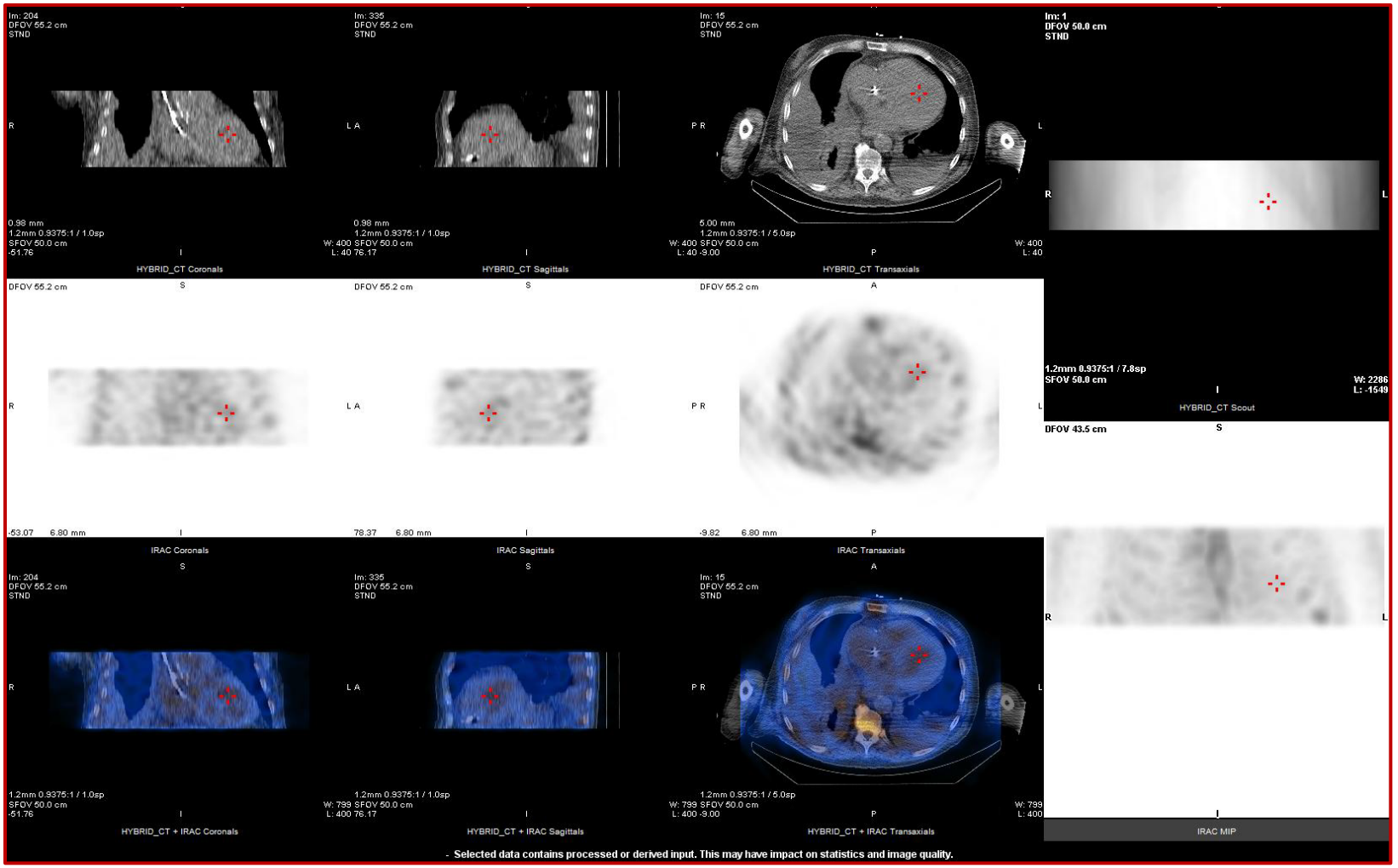
Negative Study Planar





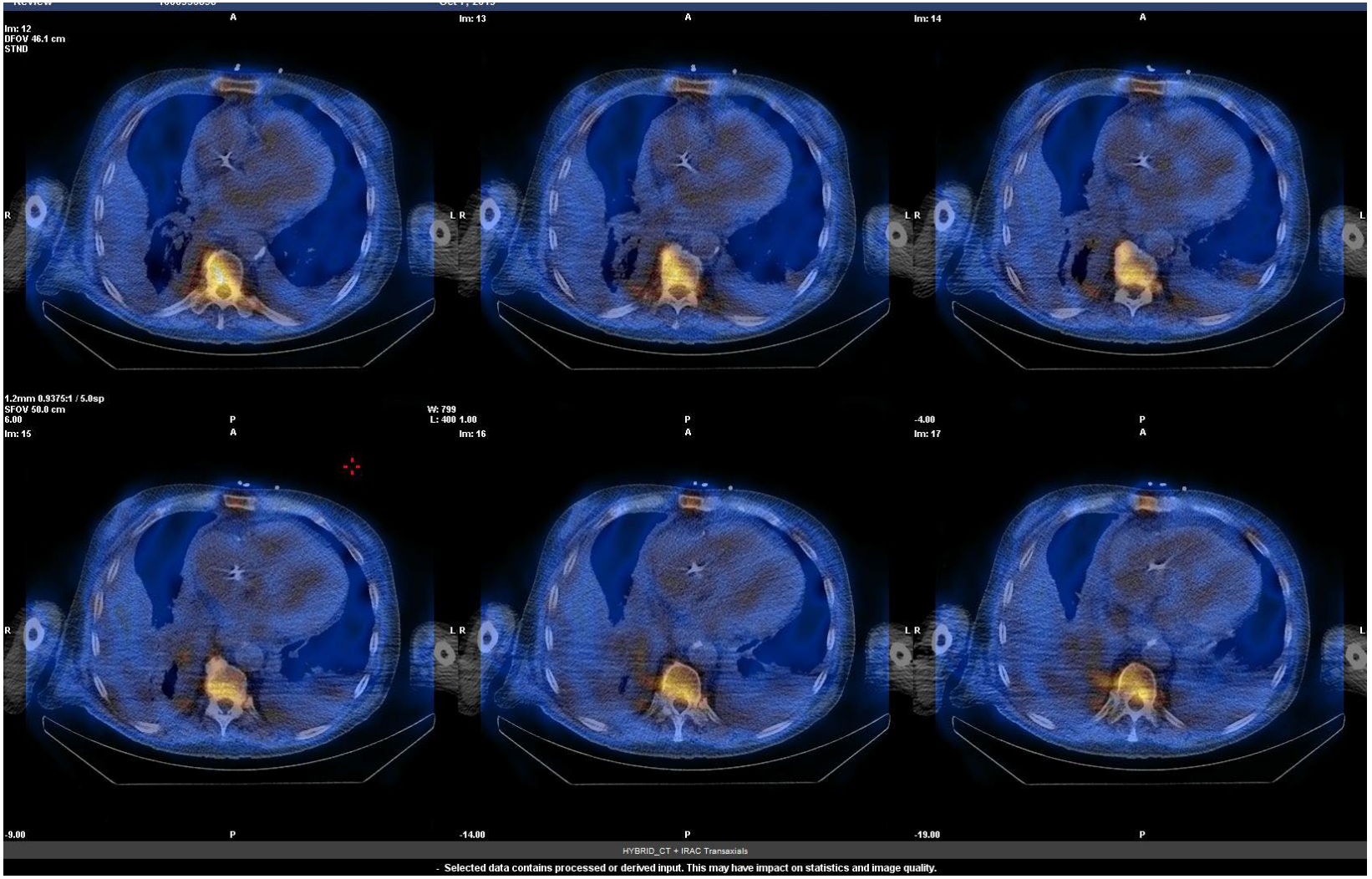
Images Courtesy of Hartford Hospital

Negative Study SPECT & CT



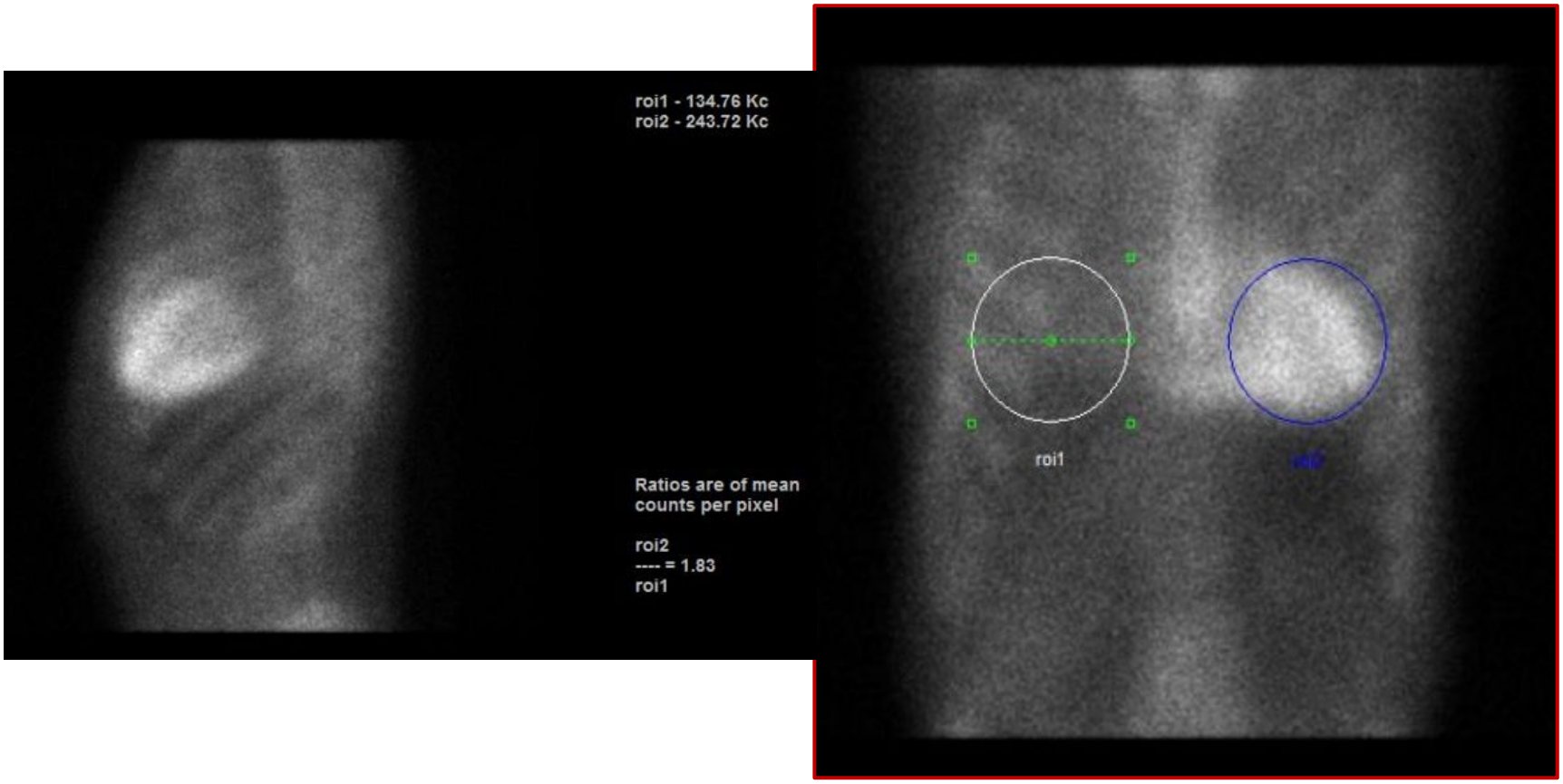
Images Courtesy of Hartford Hospital

Negative Study Fused CT



Images Courtesy of Hartford Hospital

Positive Study Planar



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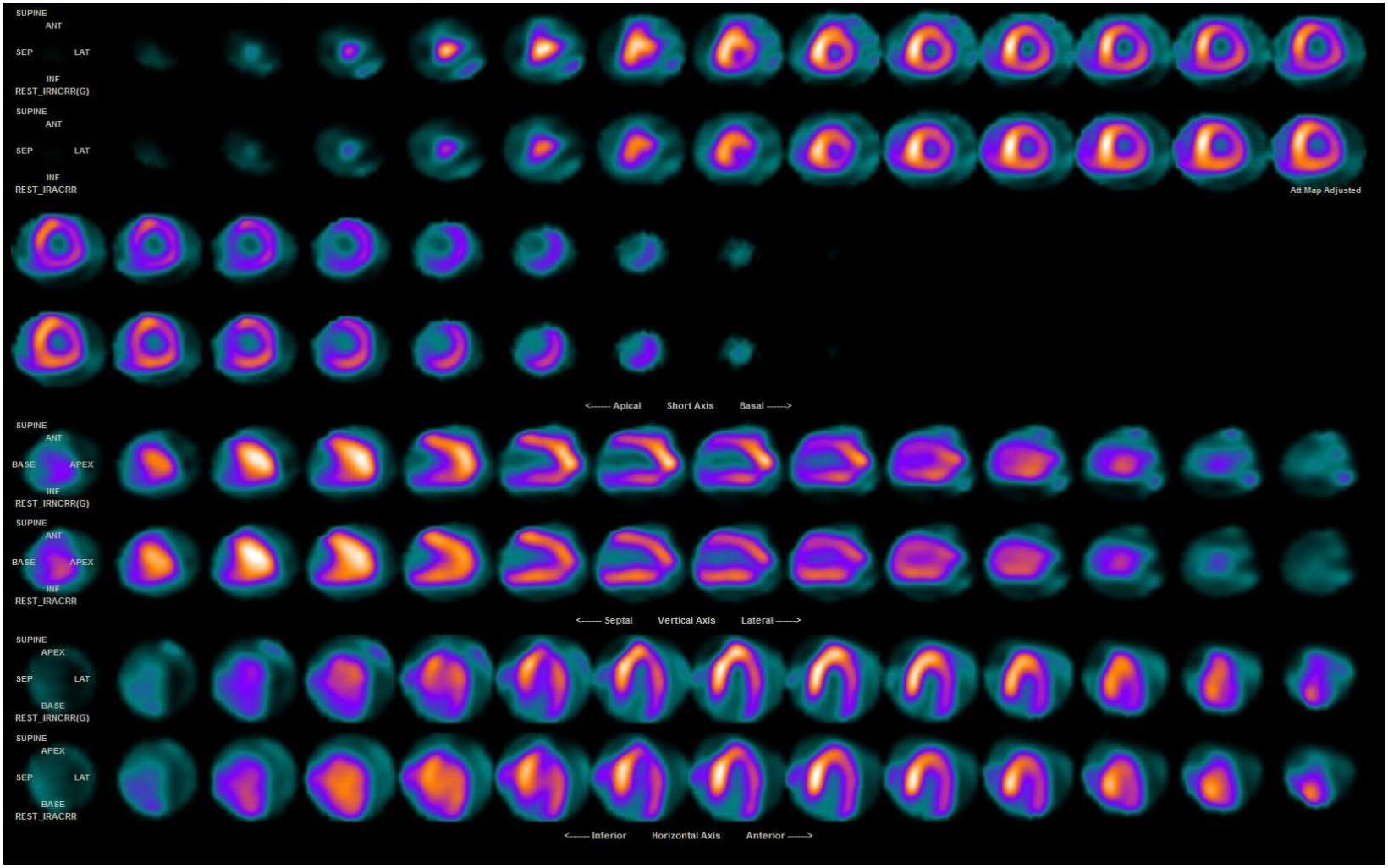
Positive Study SPECT



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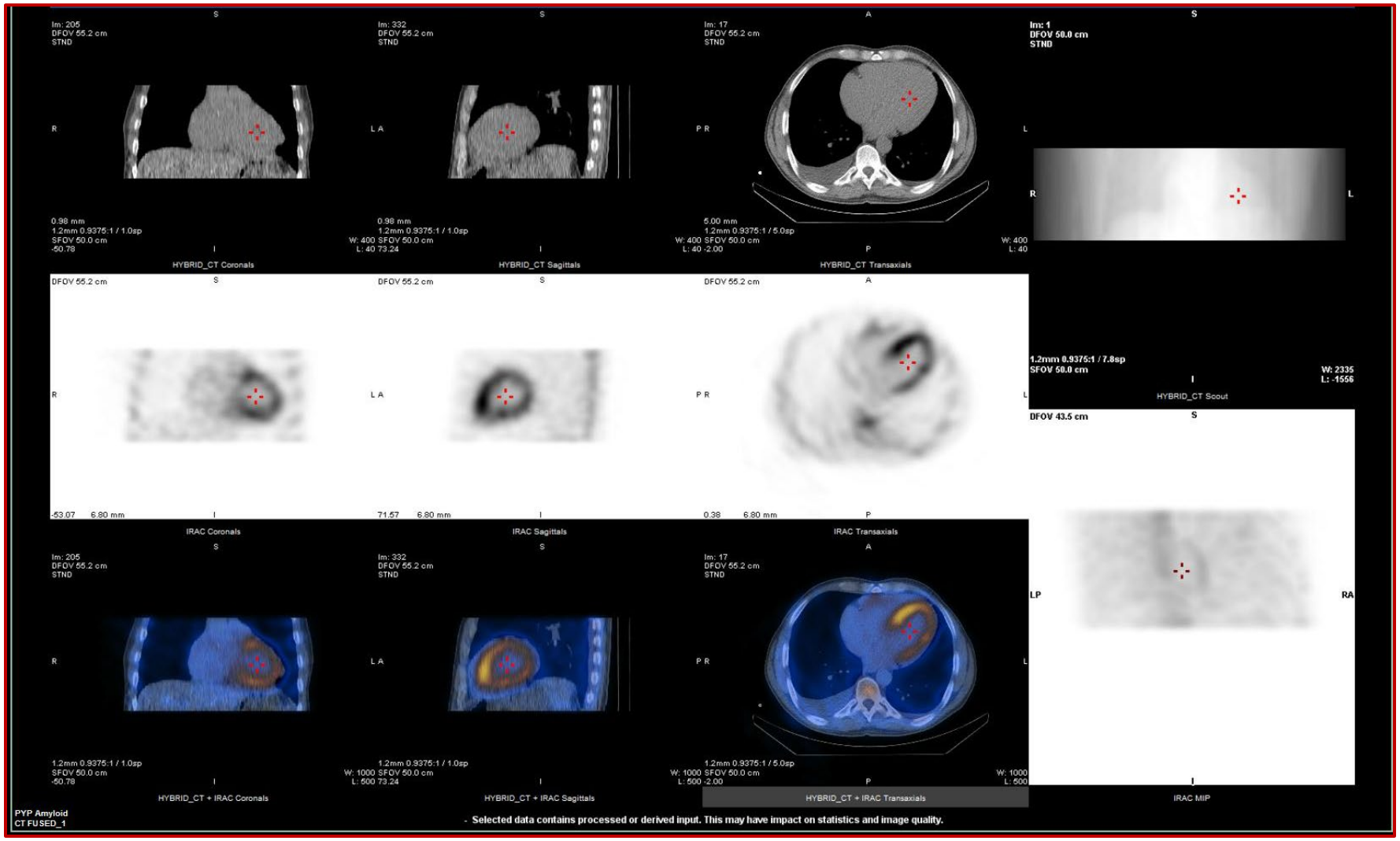
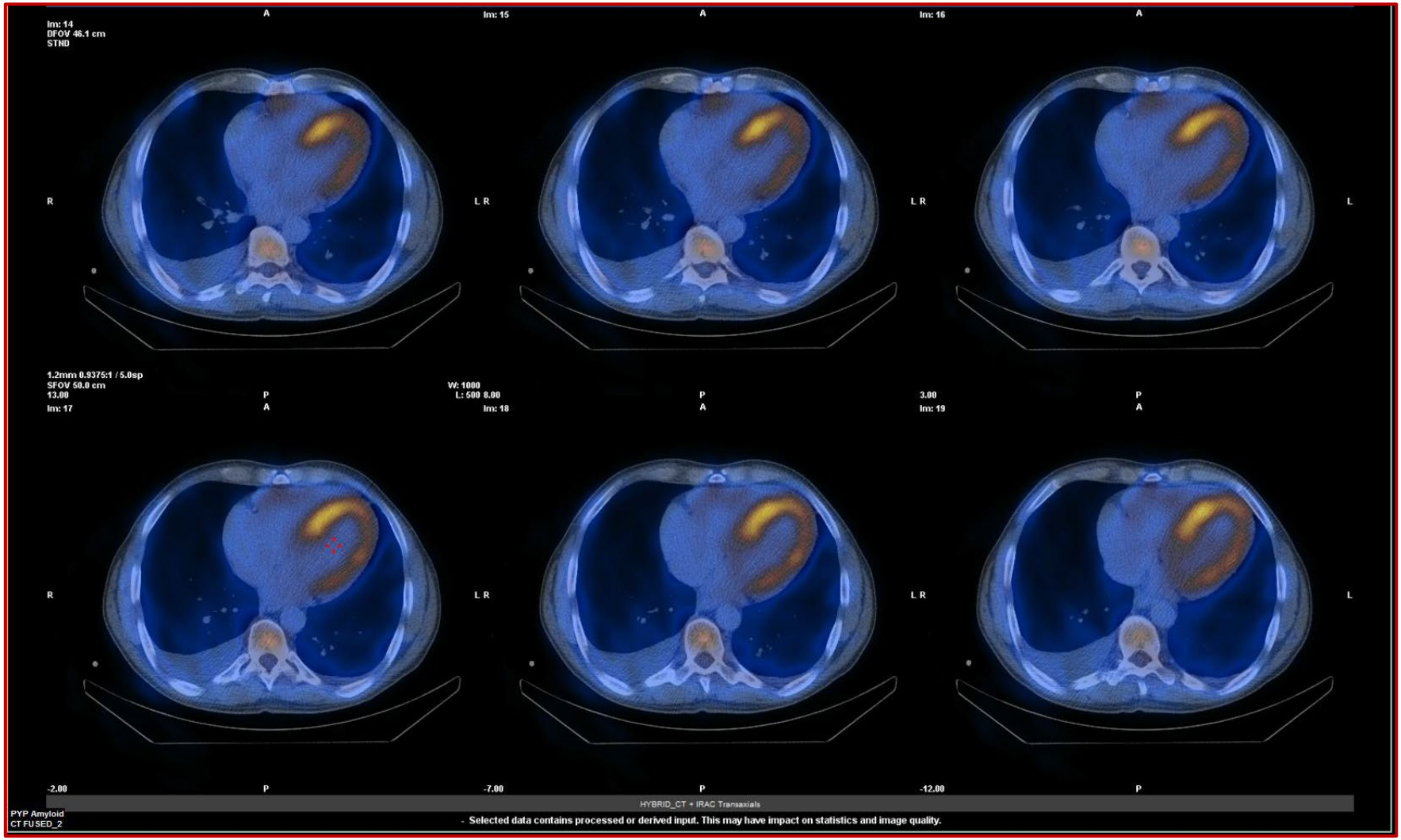
Positive Study SPECT & CT



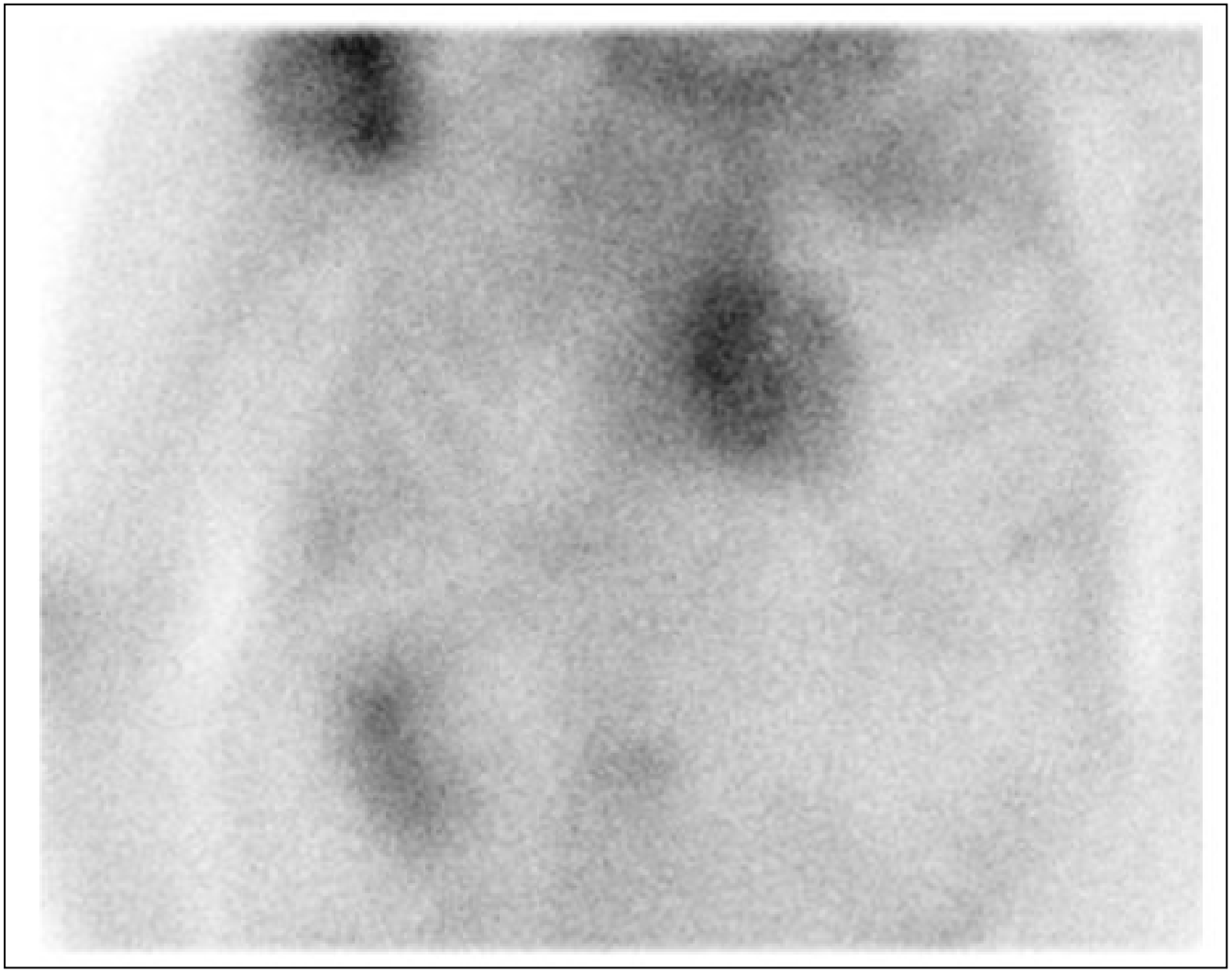
Images Courtesy of Hartford Hospital

Positive Study Fused CT



Images Courtesy of Hartford Hospital

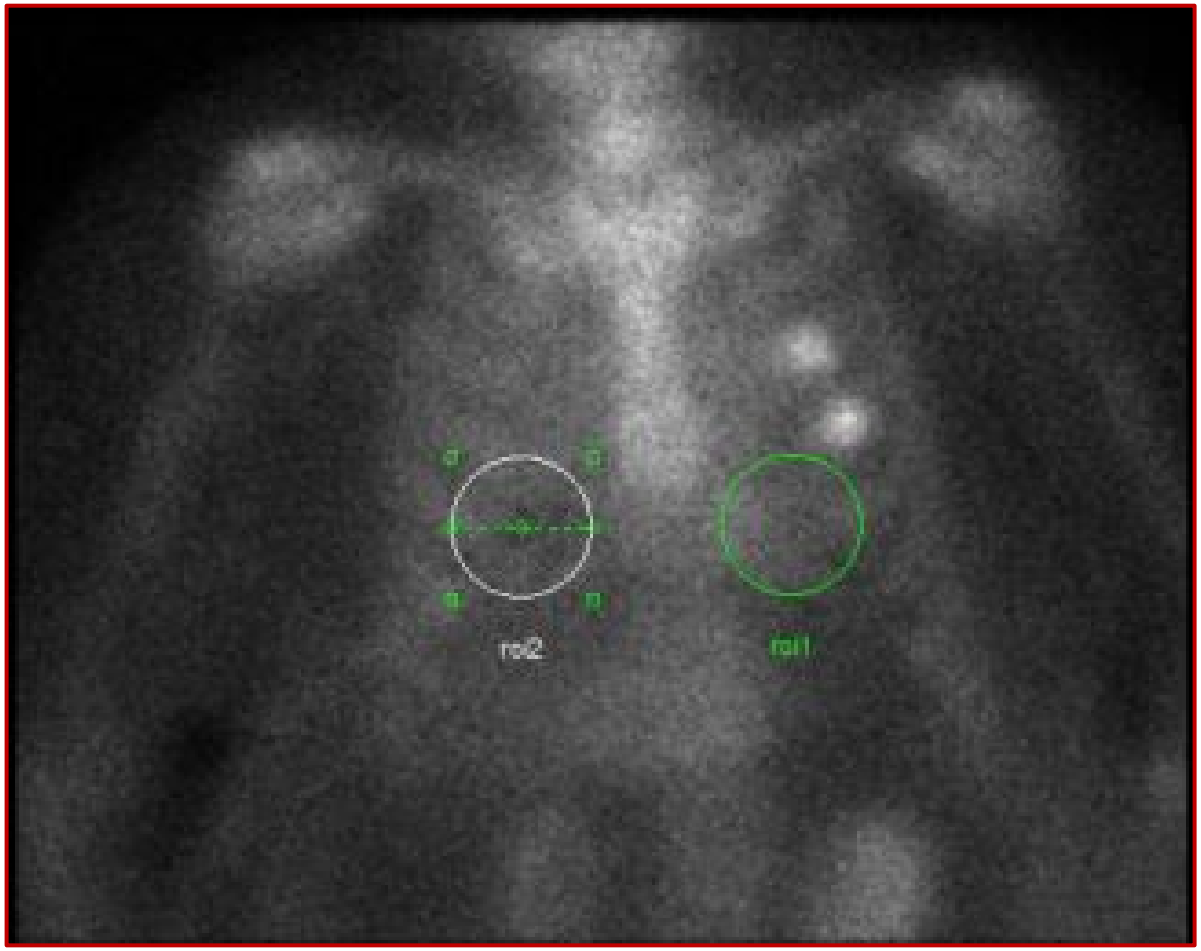
Overlying Sternum



Images Courtesy of Hartford Hospital

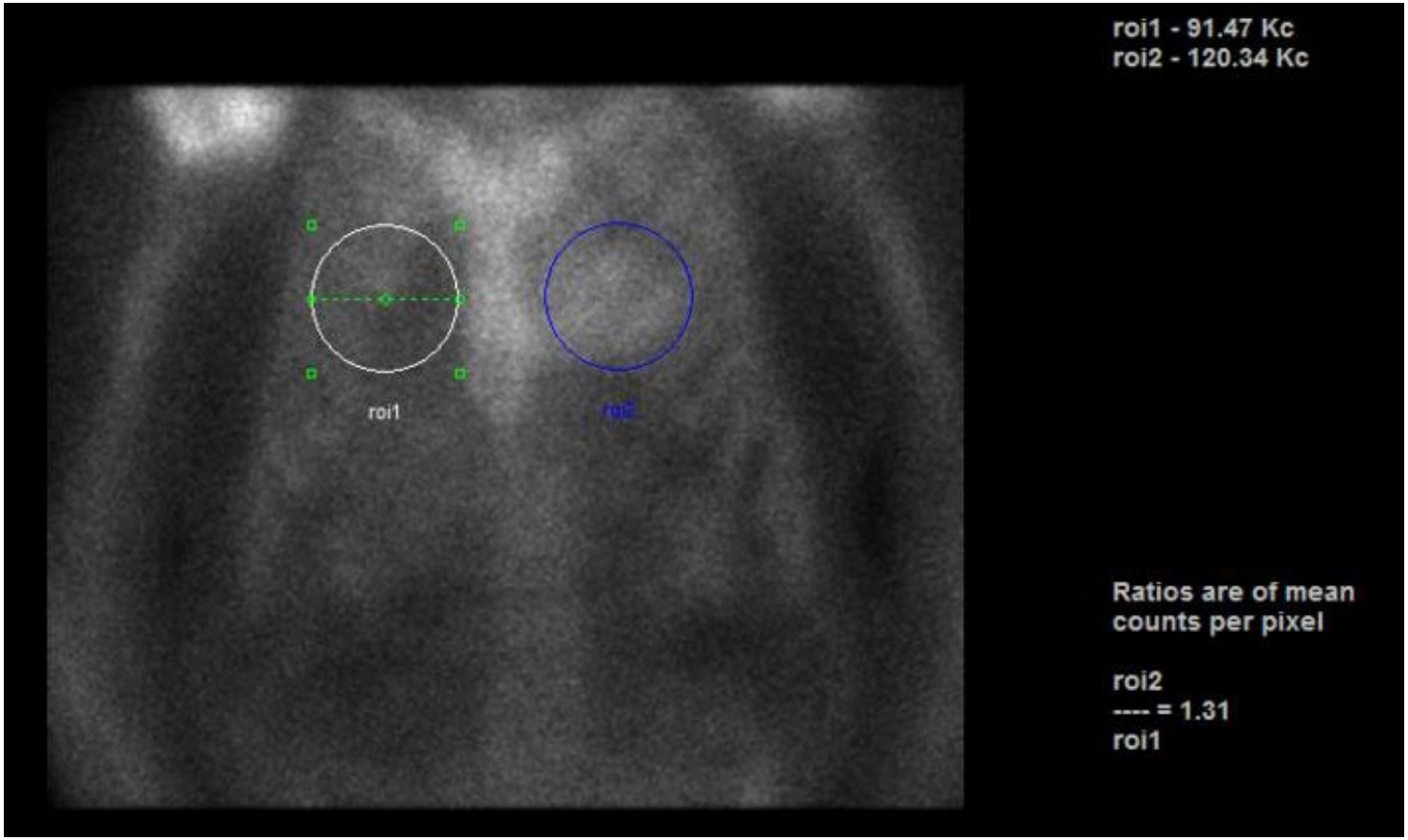
Focal Rib Uptake

Unable to correctly position the region of interest



Images Courtesy of Hartford Hospital

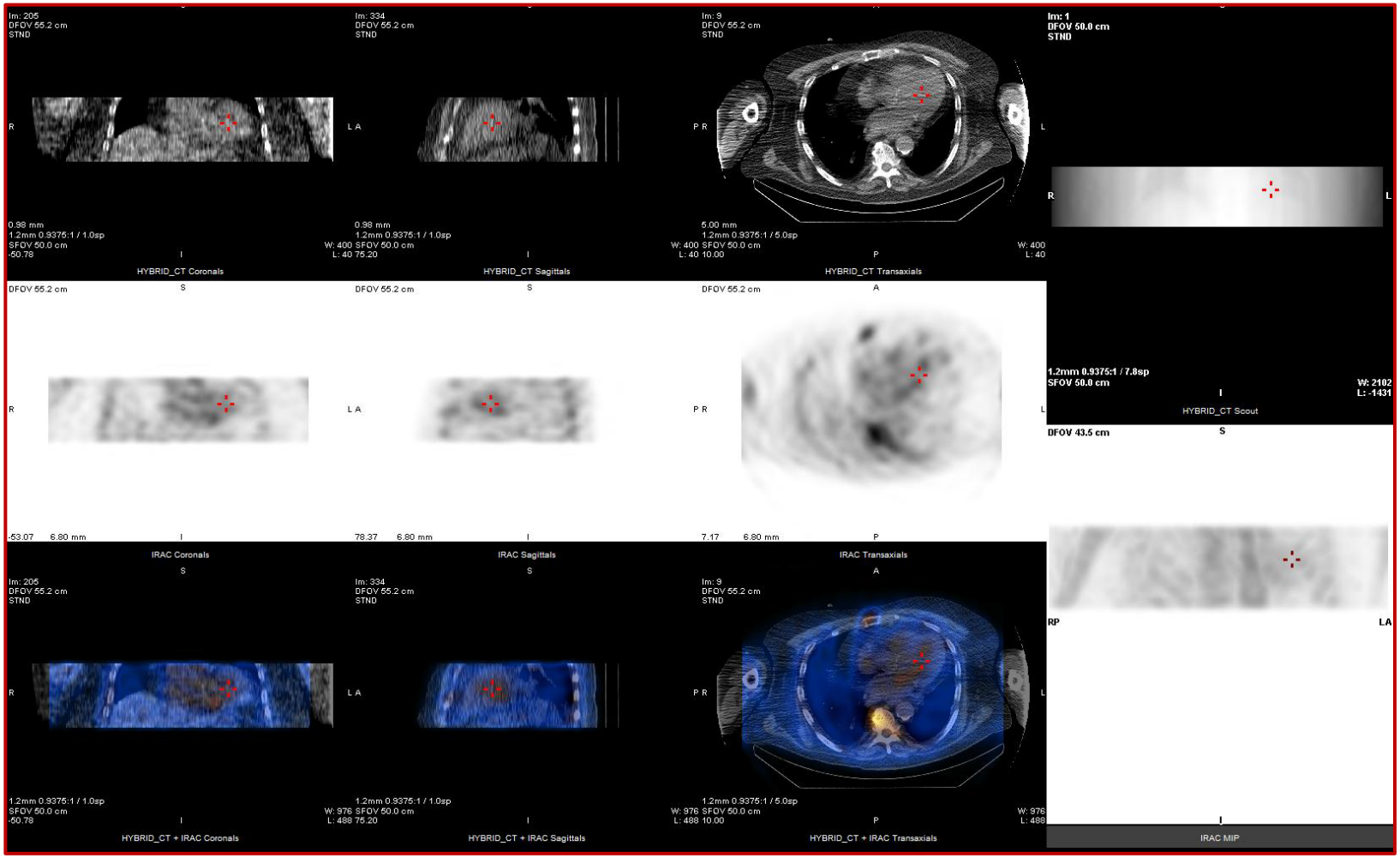
Planar – Positive or Negative?



Equivocal?

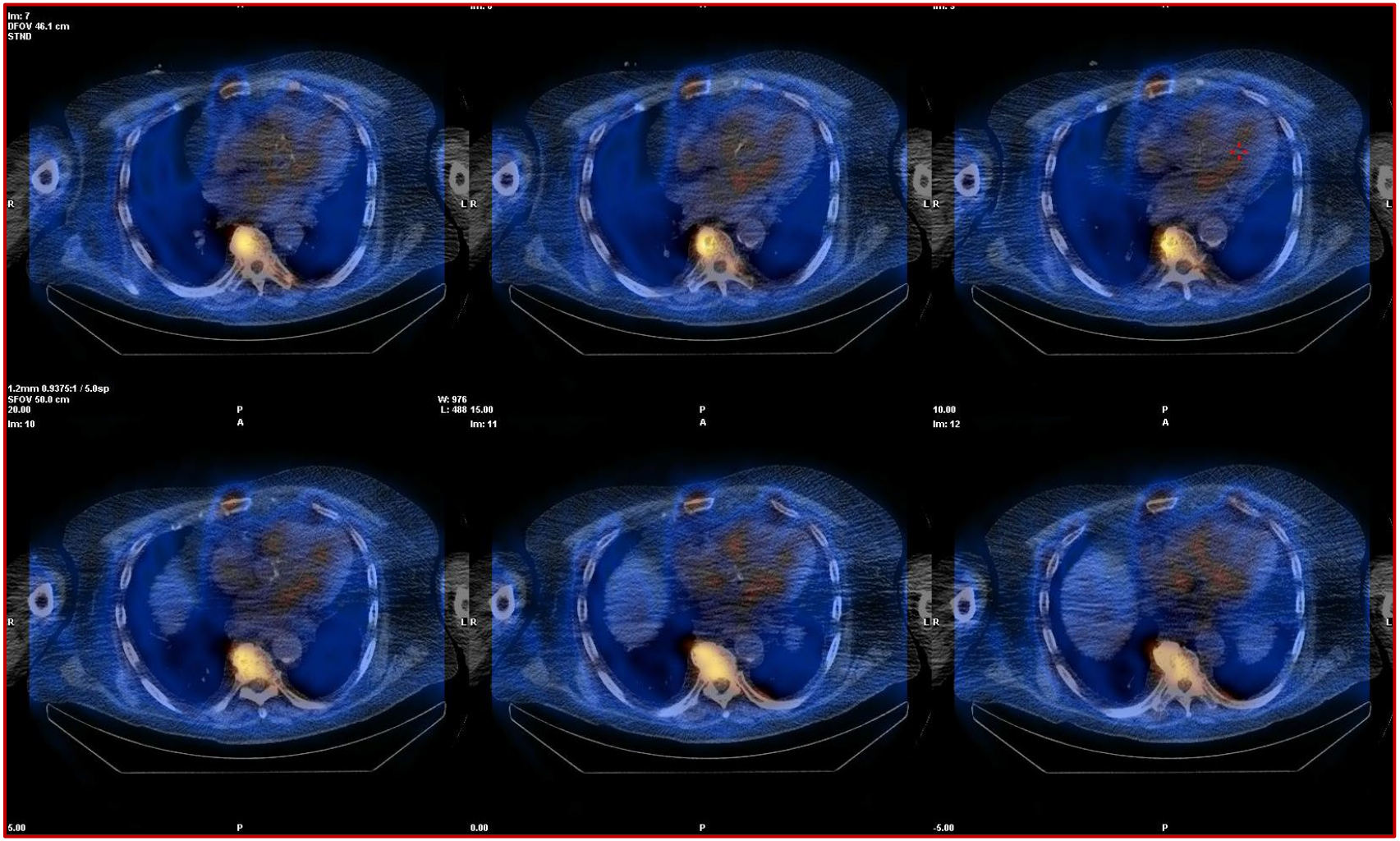
Images Courtesy of Hartford Hospital

SPECT & CT Review



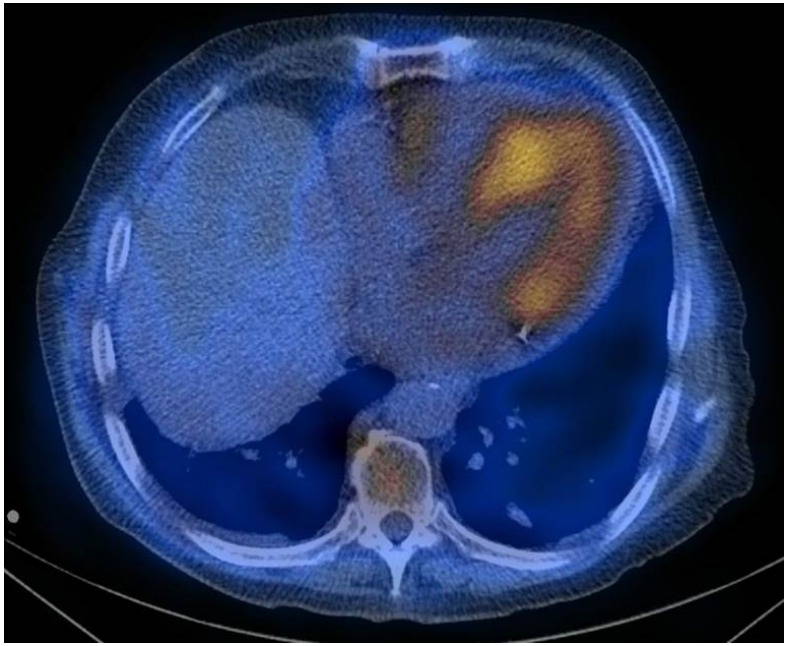
Images Courtesy of Hartford Hospital

Fused CT Review – Blood Pool

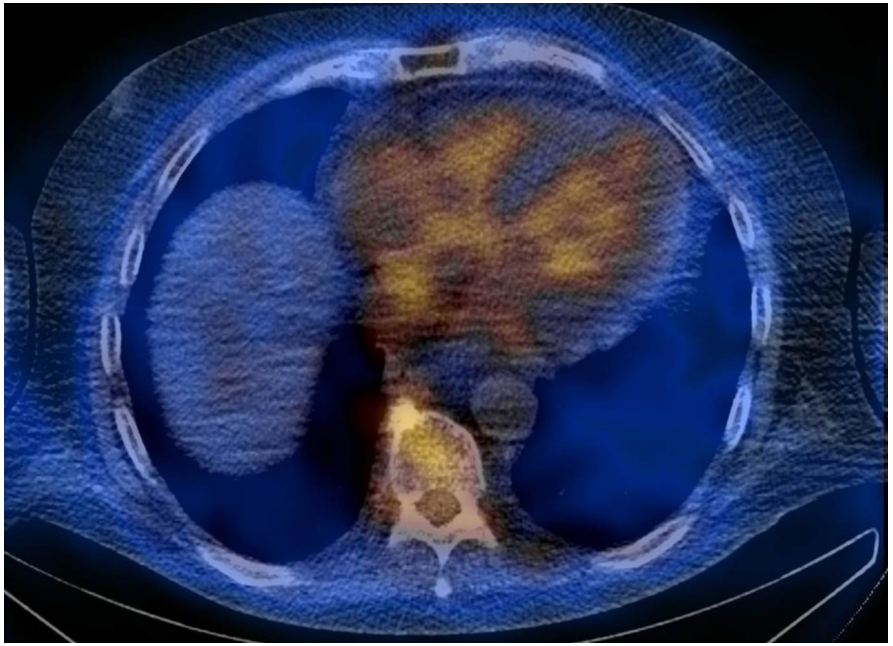


Images Courtesy of Hartford Hospital

Blood Pool Differentiation on CT



Myocardial Uptake



Blood Pool Uptake

Images Courtesy of Hartford Hospital

Summary

- Cardiac amyloidosis in an underdiagnosed cause of heart failure
- Tc-99m PYP imaging plays an important role in the non-invasive diagnosis of ATTR-CM
- Size and placement of ROI is critical
- SPECT imaging allows evaluation of residual blood pool activity
- Many labs are now recommending imaging at 3hr and SPECT Imaging as standard

Note: Tc-99m PYP scintigraphy should be interpreted in conjunction with serum and urine studies to exclude AL amyloidosis