Present and Past of Nuclear Medicine in ATTR Cardiac Amyloidosis Imaging

Annual Meeting of the Working Group on
Myocardial & Pericardial Diseases

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Disclosures for Dr. Shay Livschitz

Research Support	Spectrum Dynamics Medical
Employee	Kaplan MC
Consultant and/or Honoraria	Pfizer
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Scientific Advisory Board	

ATTR Cardiac Amyloidosis Underdiagnosis “Revolution”

- Noninvasive diagnostic tools have a limited value in the diagnosis and type identification of CA.
- Fat pad biopsy though simple, has low diagnostic yield in ATTR cardiac amyloidosis (sensitivity: 15% in wildtype ATTR, 45% in mutan ATTR).
- This is why historically, endomyocardial biopsy has been used to confirm cardiac amyloidosis and identify the fibril type.
- Recently, ***nuclear medicine cardiac imaging*** has revolutionized the field’s ability to specifically diagnose ATTR cardiac amyloidosis noninvasively, obviating the need for endomyocardial biopsy.

Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis

Julian D. Gillmore, MD, PhD; Mathew S. Maurer, MD; Rodney H. Falk, MD;

(Circulation. 2016;133:2404-2412)

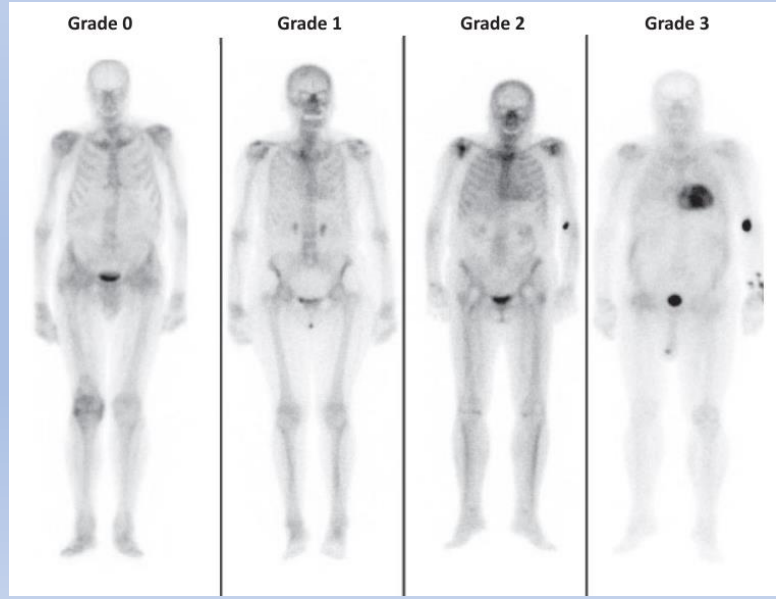
- Multicenter collaboration studied 1,217 patients referred for suspicion of CA who underwent cardiac scintigraphy with 99mTc-pyrophosphate [99mTc-PYP], 99mTc-3,3-diphosphono1,2-propanodicarboxylic acid [99mTc-DPD], and or with 99mTc-hydroxymethylene diphosphonate [99mTcHMDP]).
- According to the grading devised by Perugini 99mTc-PYP:

  grade 0=absent cardiac uptake;

  grade 1=mild uptake less than bone

  grade 2=moderate uptake equal to bone

  grade 3=high uptake greater than bone



Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis

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Radionuclide 'Bone' Scintigraphy Findings Among 374 Patients With EMBs

	^{99m}Tc-DPD Scan Findings, n				
EMB Findings	Perugini 0	Perugini 1	Perugini 2	Perugini 3	n
No cardiac amyloid	31	3	0	1	35
Cardiac ATTR amyloid deposits	1	8	130	23	162
Cardiac AL amyloid deposits	21	13	7	2	43
Cardiac ApoAI amyloid deposits	0	2	0	0	2
Cardiac amyloid deposits of unknown type	1	1	0	0	2
Total	54	27	137	26	244
	^{99m}Tc-PYP Scan Findings				
	Grade 0	Grade 1	Grade 2	Grade 3	n
No cardiac amyloid	7	1	1	0	9
Cardiac ATTR amyloid	1	10	7	67	85
Cardiac AL amyloid deposits	10	1	3	1	15
Cardiac ApoAI amyloid deposits	0	0	0	0	0
Cardiac amyloid deposits of unknown type	0	0	0	0	0
Total	18	12	11	68	109
	^{99m}Tc-HMDP Scan Findings				
	Grade 0	Grade 1	Grade 2	Grade 3	n
No cardiac amyloid	3	0	0	0	3
Cardiac ATTR amyloid deposits	0	3	4	7	14
Cardiac AL amyloid deposits	4	0	0	0	4
Cardiac ApoAI amyloid deposits	0	0	0	0	0
Cardiac amyloid deposits of unknown type	0	0	0	0	0
Total	7	3	4	7	21

Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis

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	Positive Scan (Grade 1, 2, or 3), n	Negative Scan (Grade 0), n	
Cardiac ATTR amyloid deposits	259	2	>99 (97–100) sensitive
No cardiac ATTR amyloid deposits	36	77	68 (59–77) specific

- The low specificity (68%) of a positive scan (grades 1-3) for cardiac ATTR amyloid deposits was due almost entirely to cardiac uptake of tracer among patients with cardiac AL or cardiac apolipoprotein A-I amyloidosis.

	Grade 2/3 Scan, n	Grade 0/1 Scan, n	
Cardiac ATTR amyloid deposits	238	23	91 (87–94) sensitive
No cardiac ATTR amyloid deposits	15	98	87 (79–92) specific

- The specificity for cardiac ATTR amyloid of grade 2 or 3 cardiac uptake on radionuclide imaging increases to ≈87%, but the sensitivity falls to 91%

- The specificity and positive predictive value for cardiac ATTR amyloid of the combination of **grade 2 or 3 cardiac** uptake on a radionuclide scan and the **absence of a detectable monoclonal protein** were 100% (positive predictive value confidence interval, 99.0–100%) in this cohort of 1217 patients and were also 100% among each of the 3 different radiotracer cohorts

Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis

"Cardiac ATTR amyloidosis can be reliably diagnosed in the absence of histology provided that all of the following criteria are met:

- heart failure with an echocardiogram or CMR that is consistent with or suggestive of amyloidosis,
- grade 2 or 3 cardiac uptake on a radionuclide scan with 99mTc-DPD, 99mTcPYP, or 99mTc-HMDP,
- absence of a detectable monoclonal protein"

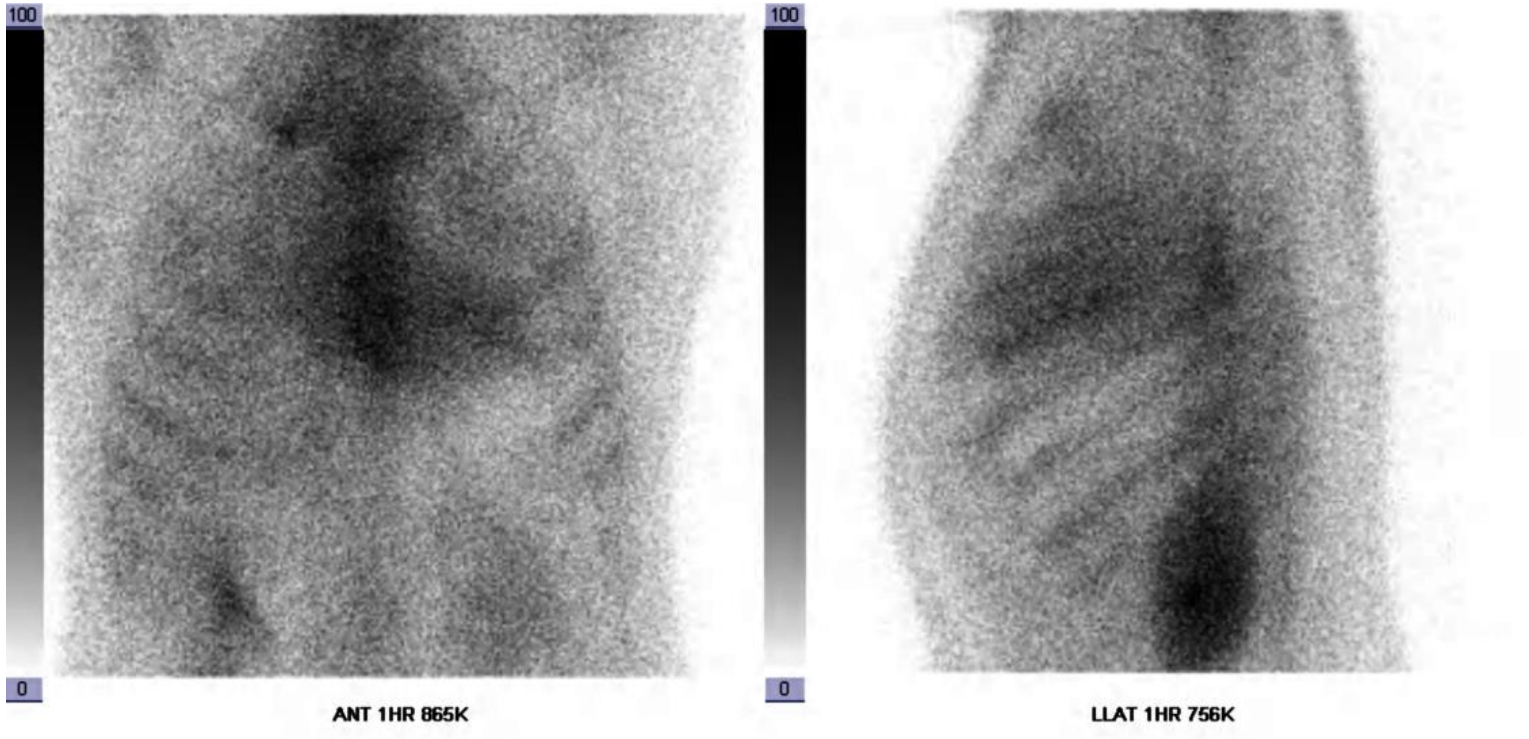
The *high test performance* characteristics were favorably skewed owing to the high pre-test likelihood in the study cohort.

Nonbiopsy Diagnosis of Transthyretin Cardiac Amyloidosis

- Thanks to advances in imaging techniques and the possibility of achieving a non-invasive diagnosis, we now know that cardiac amyloidosis is a more frequent disease than traditionally considered.
- These early studies showed “high-diagnostic accuracies” leading to great excitement in the field and a profusion of studies.

First Author	Radiotracer	N	Cohort	Prevalence of ATTR
Gonzalez-Lopez[38]	^{99m}Tc-DPD	120	Heart failure with preserved EF Hospitalized patients 42% women	13.3%
Castano[39]	^{99m}Tc-PYP	151	TAVR Age > 75 years Severe aortic stenosis Low flow low gradient AS Mean LVEF 46%	16%
Haq[36]	^{99m}Tc-PYP		Hereditary ATTR No heart failure Normal echocardiogram Normal cardiac biomarkers	83%
Bennani-Smires[37]	^{99m}Tc-DPD	49	Age > 65 years Heart failure with preserved EF	18%
Longhi S[56]	^{99m}Tc-DPD	43	Aortic stenosis 5 with echo red flags underwent ^{99m}Tc-DPD and all were strongly positive	11.6%
Longhi S[41]	^{99m}Tc-DPD	12400	All bone scans performed over a 5 + year period for clinical reasons	0.36%
Mohamed-Salem[42]	^{99m}Tc-DPD	1114	Age ≥ 75 years Bone scan for clinical reasons	2.78%
Sperry[40]	^{99m}Tc-PYP	98	Carpal tunnel surgery Men ≥ 50 years Women ≥ 60 years 10 patients with biopsy proven amyloid from carpal tunnel procedure were evaluated by ^{99m}Tc-PYP	10.2%

TTR Cardiac Amyloidosis Planar Imaging-PYP Tc-99m scan



Patient History:

Male, 60Y

NIDDM

HTN

CLBBB

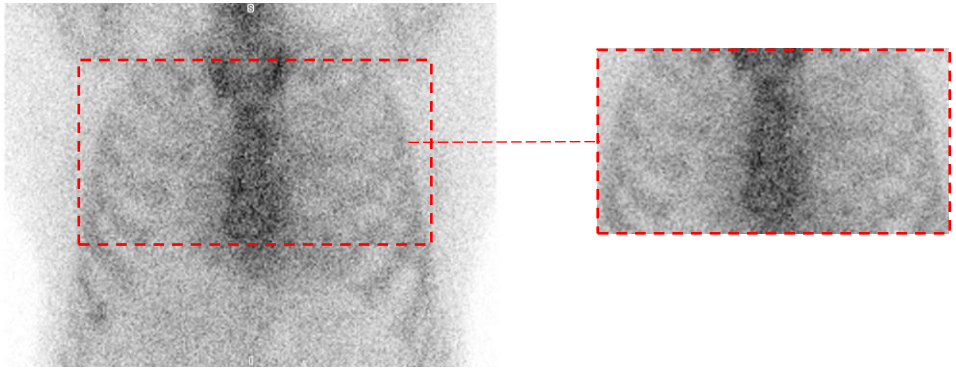
Dilated CMP

True or false positive TTR-CA?

Where the uptake is?

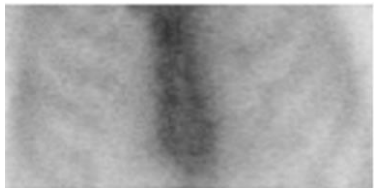
TTR Cardiac Amyloidosis Planar Imaging-PYP Tc-99m scan

Anger Planar

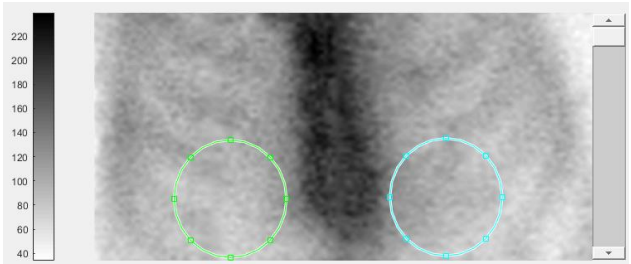


10mCi Tc-99m PYP

D-SPECT Planar



20mCi Tc-99m PYP



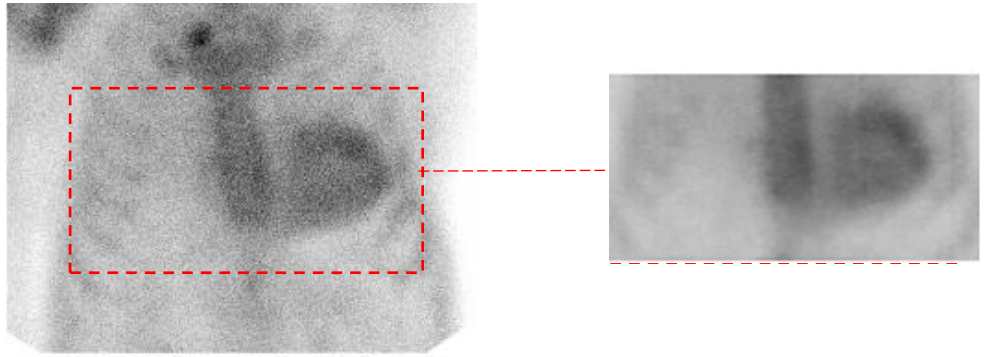
H/Clt ratio =1.0

Tshori S, Livschitz S, Volodarsky I, Goland S, Shimoni S, Fabrikant J, George J J Nucl Cardiol. 2021 **Transthyretin Cardiac Amyloidosis Scintigraphy Using Planar D-SPECT on Dedicated Cardiac CZT Camera**

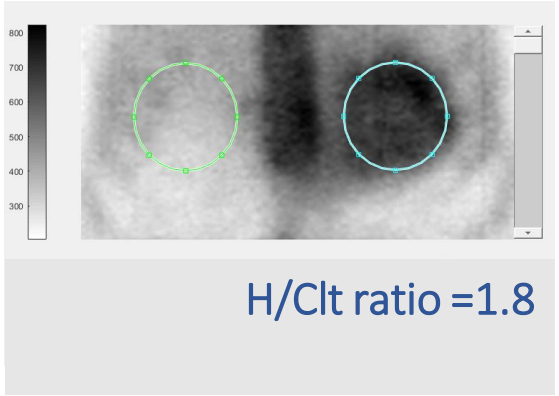
TTR Cardiac Amyloidosis Planar Imaging-PYP Tc-99m scan

Anger Planar

D-SPECT Planar



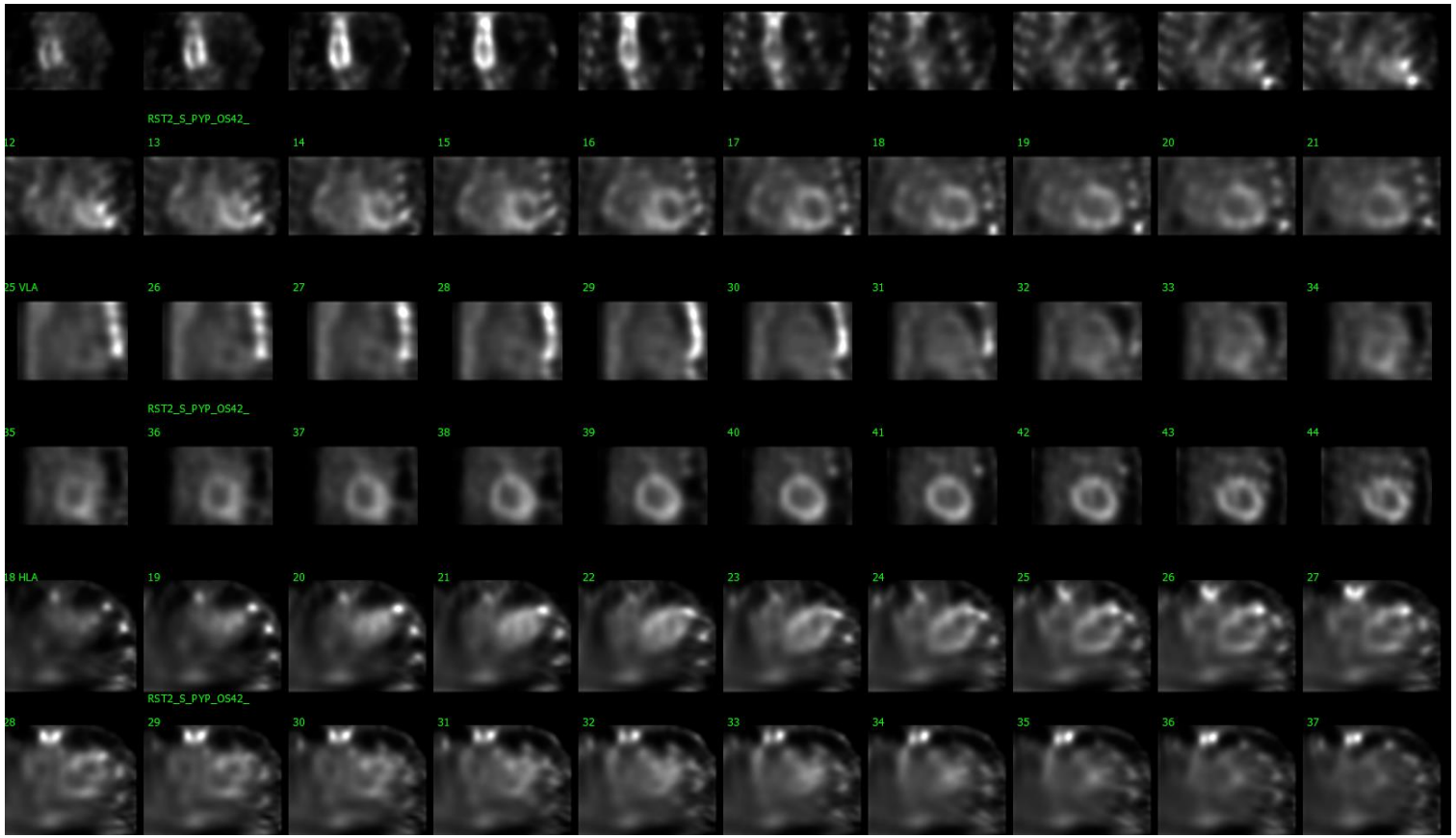
10mCi Tc-99m PYP



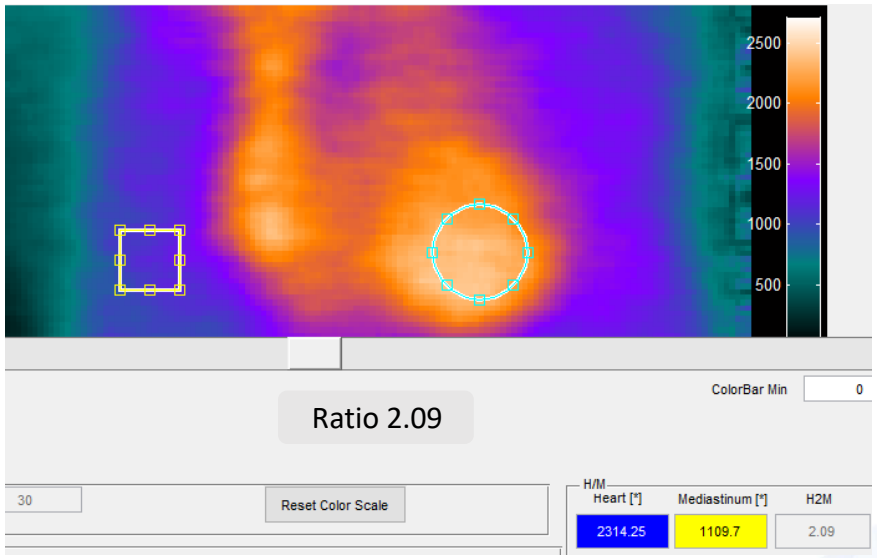
H/Clt ratio =1.8

Patient History: Male, 80Y
Indication: hypertension, hypercholesterolemia
S/P CABG + AVR
Chronic atrial fibrillation
Heart failure with systolic dysfunction (EF 35%)
NYHA III

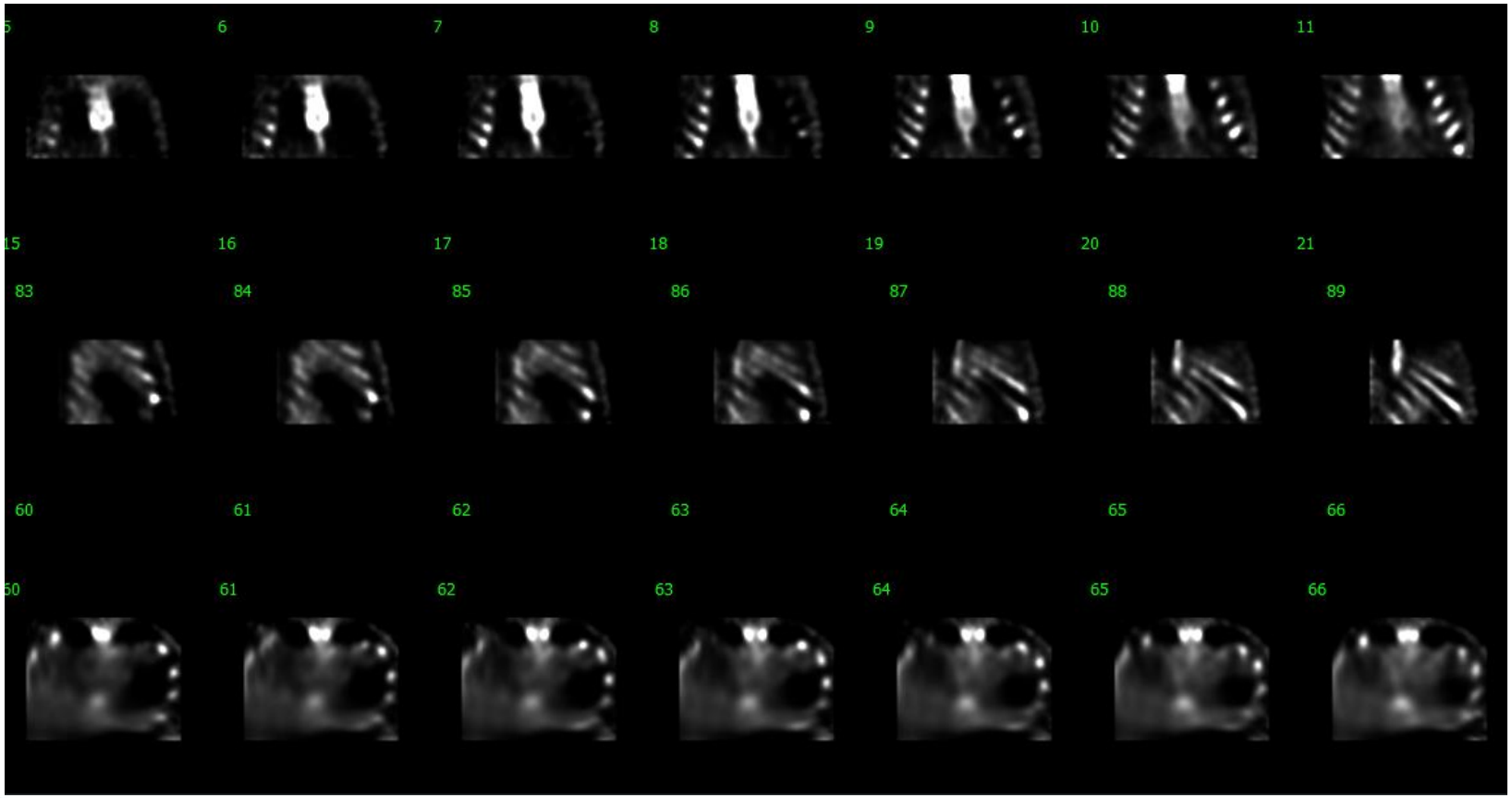
TTR Cardiac Amyloidosis PYP Tc-99m scan – D-SPECT



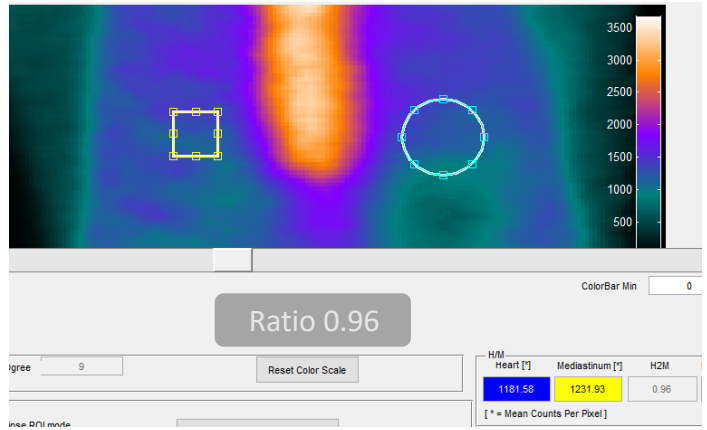
Patient History: Male,73Y
Indication: hypertension, hyperlipidemia, carpal tunnel syndrome
Findings: Positive TTR
Acquisition time: 10 min
Injected Dose: 20Mci



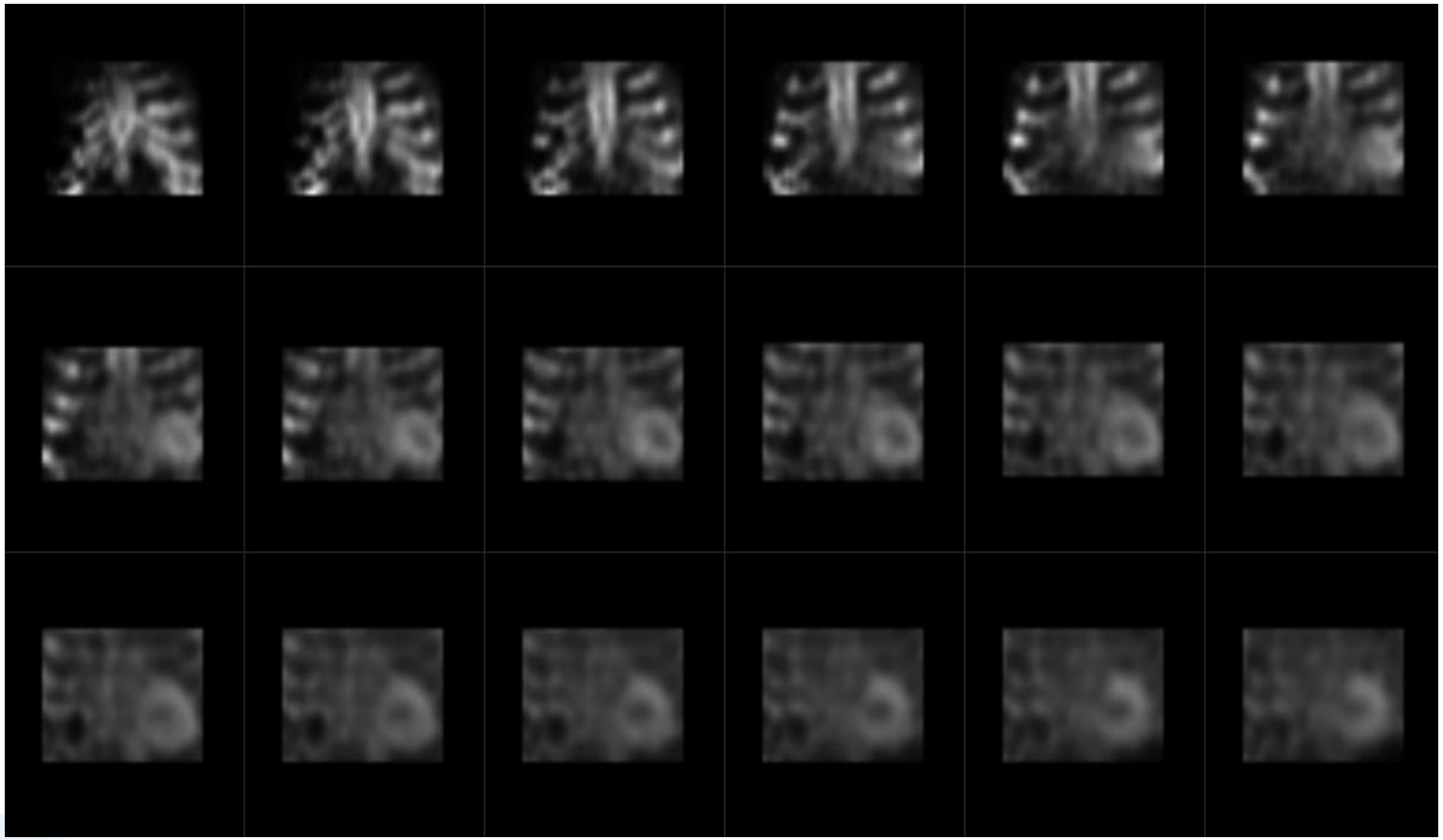
TTR Cardiac Amyloidosis PYP Tc-99m scan – D-SPECT

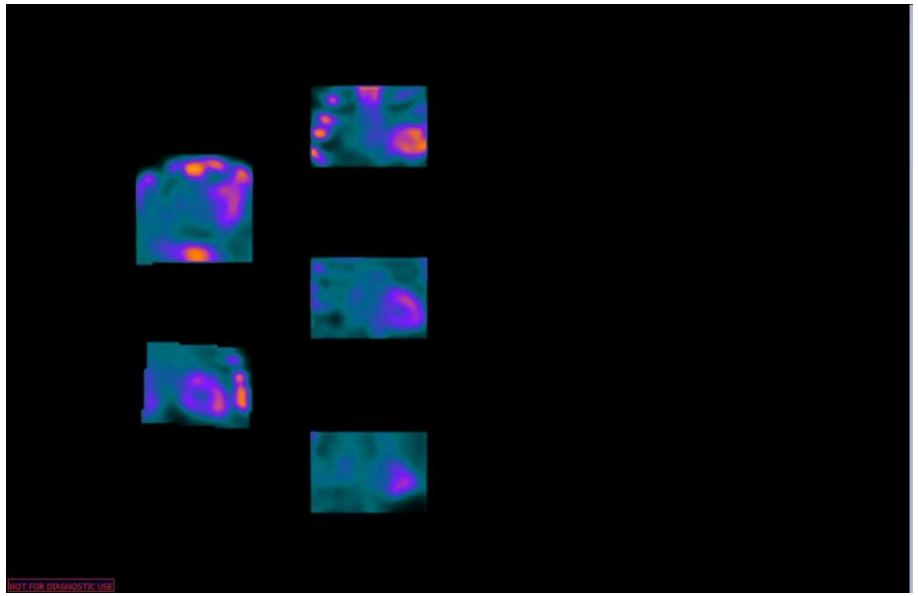


Patient History: Male, 44Y
Indication: Multiple sclerosis, numbness
Findings: Negative TTR
Acquisition time: 10 min
Injected Dose: 20Mci



TTR Cardiac Amyloidosis Positive – SPECT PYP Tc-99m scan

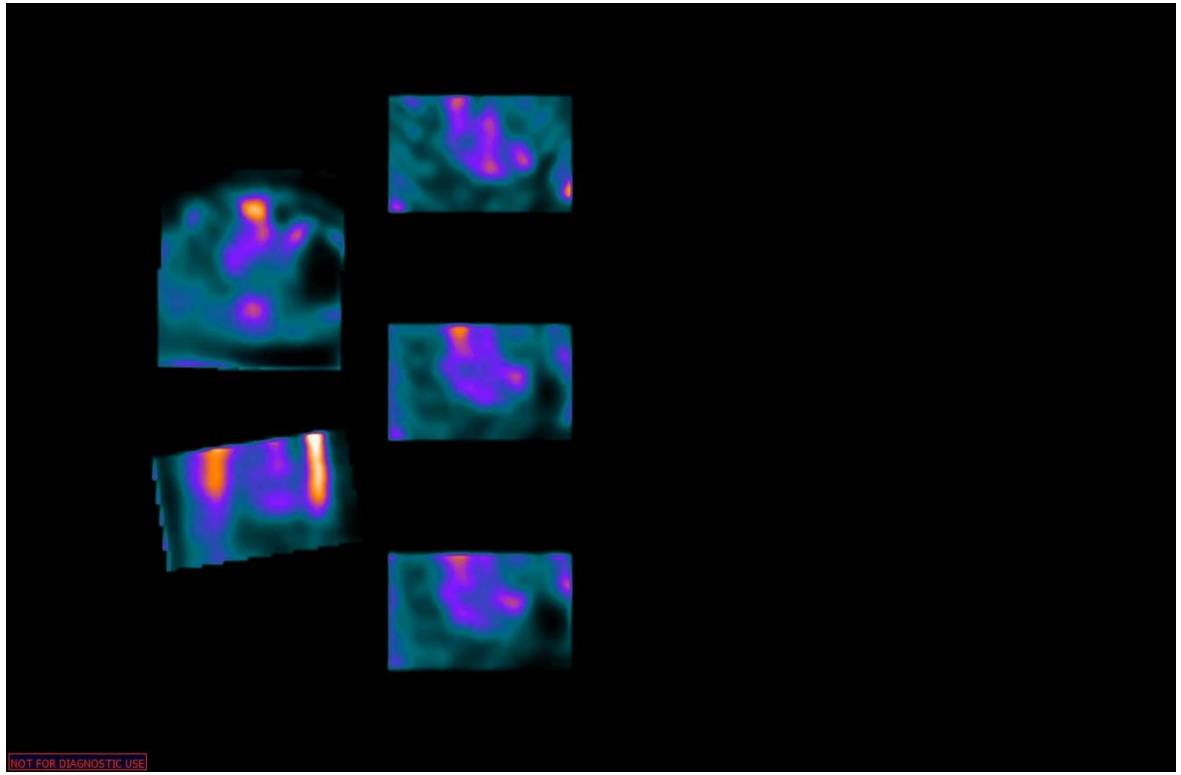




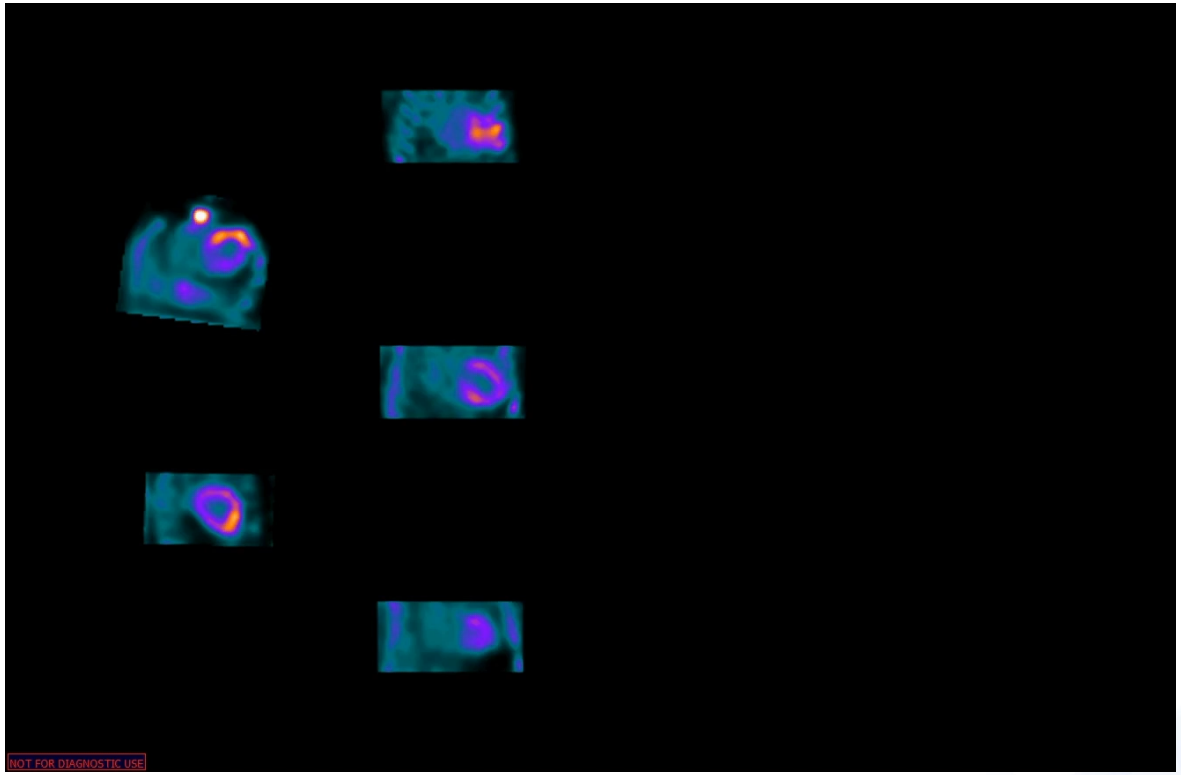
Patient History: Male, 75Y
Indication: hypertension, hypercholesterolemia, CVA
Heart failure without systolic dysfunction (EF 55%)
Suspected restrictive CMP at echo
Moderate to severe MR
Severe PHT
Acquisition time: 5 min
Injected Dose: 20 Mci

PYP Tc-99m SPECT Gated Imaging

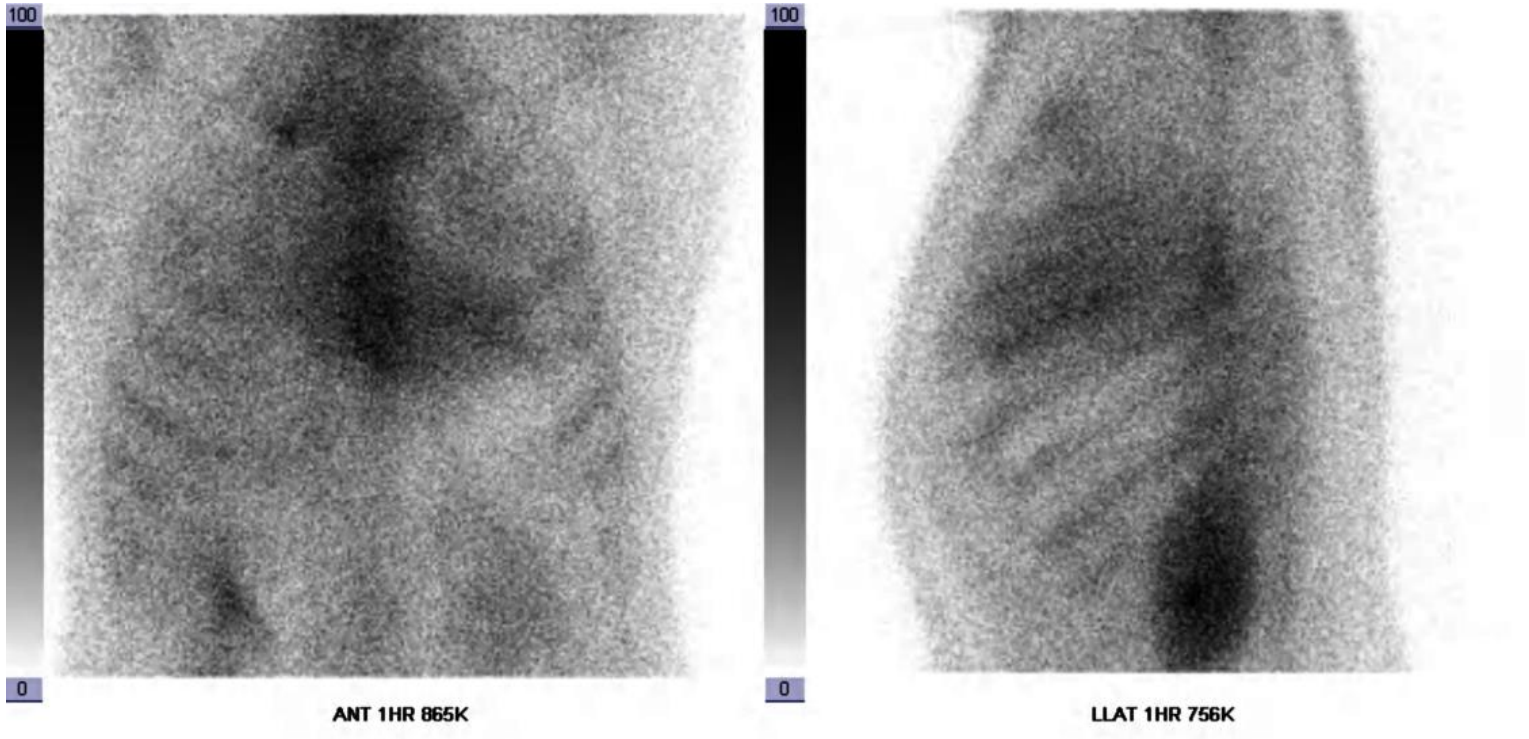
Blood Pool Imaging



TTR Cardiac Amyloidosis



TTR Cardiac Amyloidosis Planar Imaging-PYP Tc-99m scan



Patient History:

Male, 60Y

NIDDM

HTN

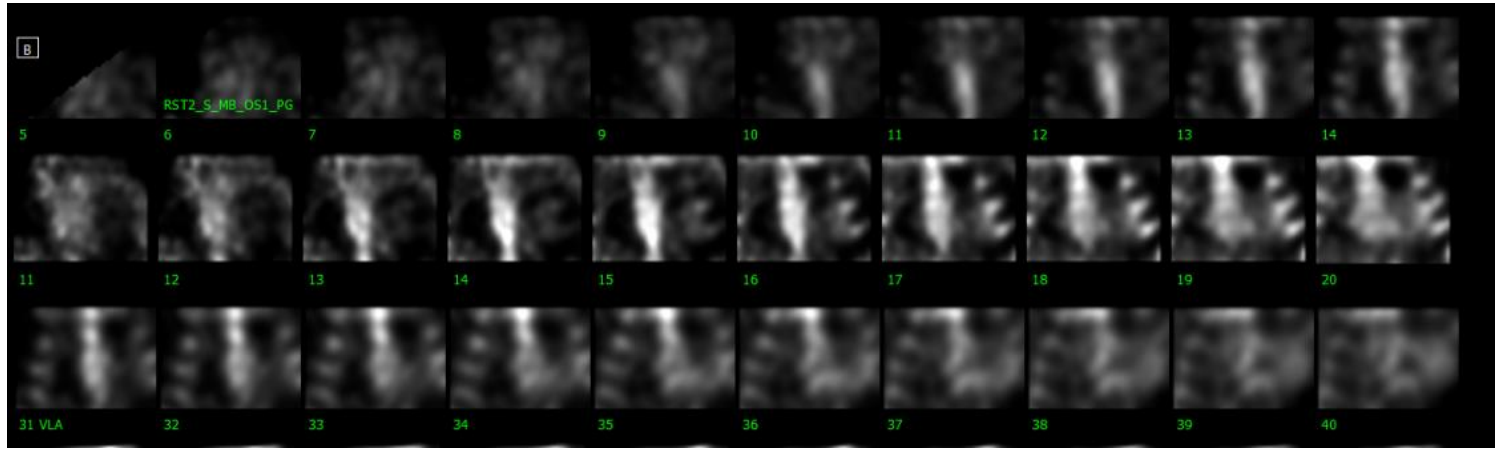
CLBBB

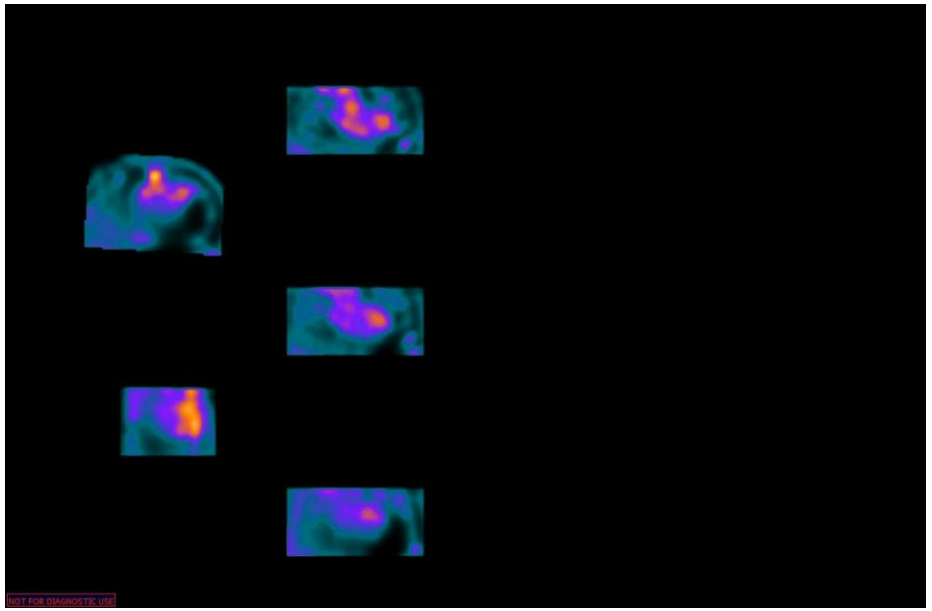
Dilated CMP

True or false positive TTR-CA?

Where the uptake is?

TTR Cardiac Amyloidosis – Gated SPECT PYP Tc-99m scan

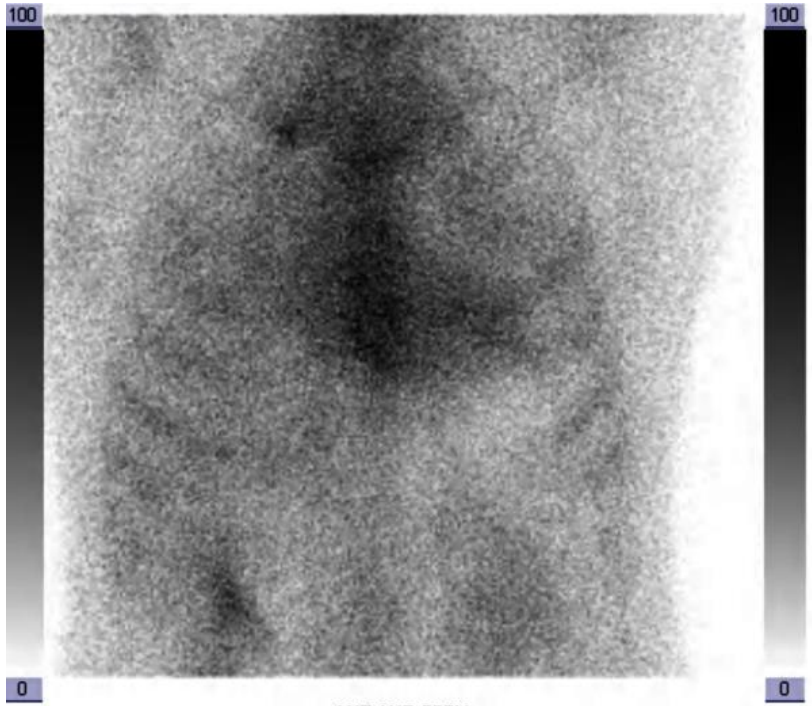


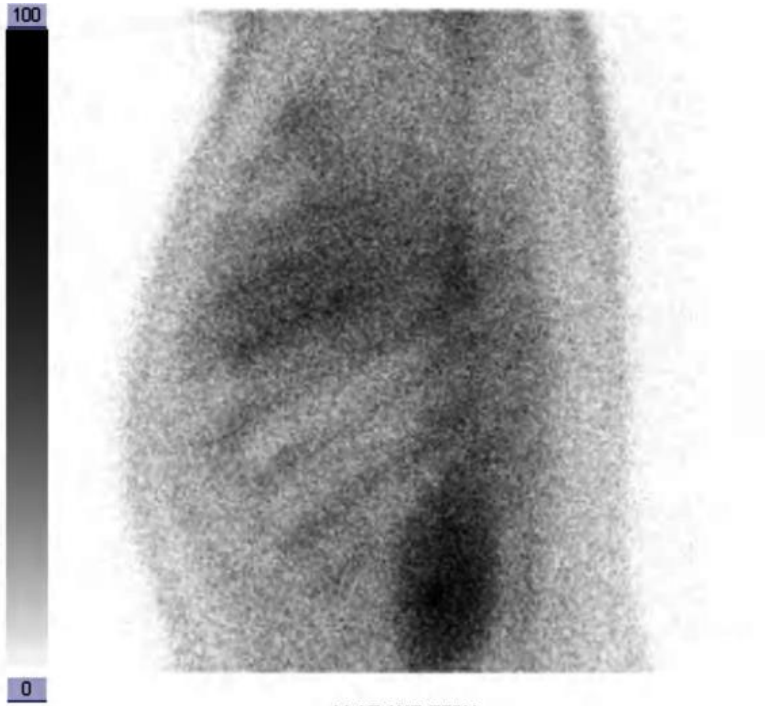


Blood Pool Imaging

Patient History: Male, 60Y
NIDDM
HTN
CLBBB
Dilated CMP
Acquisition time: 10 min
Injected Dose: 20 Mci

TTR Cardiac Amyloidosis Planar Imaging-PYP Tc-99m scan





Patient History:

Male, 60Y

NIDDM

HTN

CLBBB

Dilated CMP

True or false positive TTR-CA? **False**

Where the uptake is? **Blood pool**

Planar imaging alone is limited as myocardial uptake cannot be discerned from blood pool uptake, overlying rib uptake may add counts to the region of the heart.

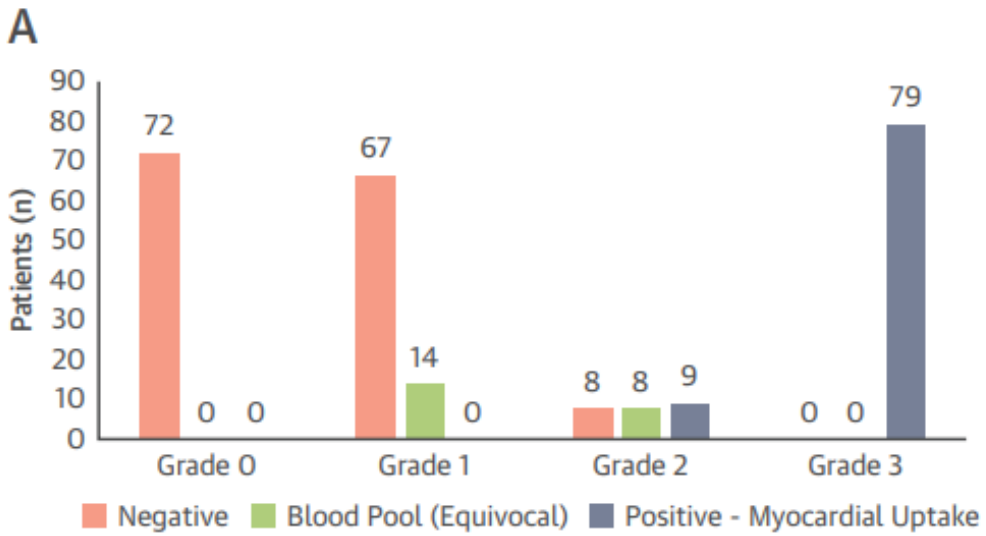
Diagnosing Transthyretin Cardiac Amyloidosis by Technetium Tc 99m Pyrophosphate

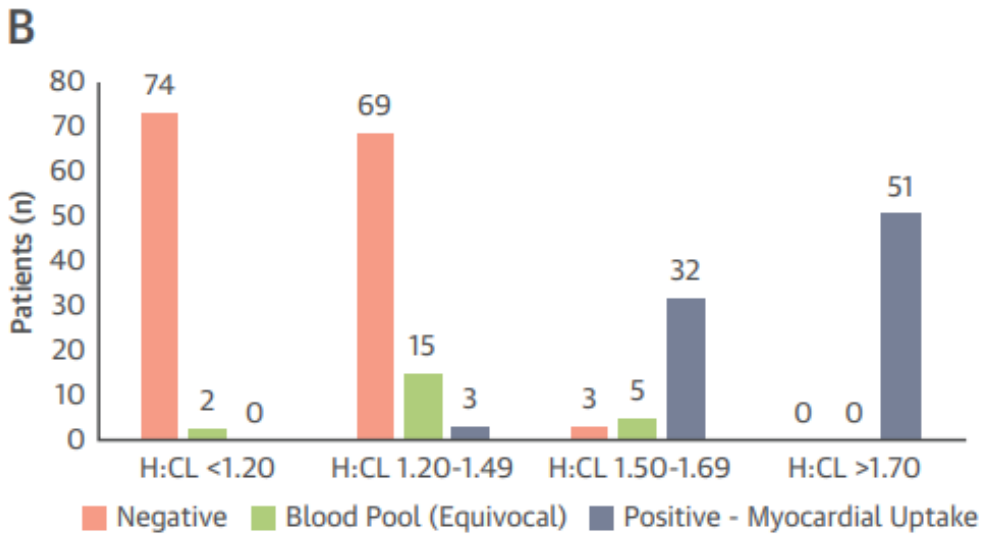
Poterucha et al .JACC: CARDIOVASCULAR IMAGING, VOL. 14, NO. 6, 2021

- A total of 753 unique patients underwent 99mTc-PYP scanning at Columbia University Irving Medical Center were included in this study.
- Standardized imaging protocol with 99mTc-PYP imaged at 1 h after injection

	Total Patients (N = 753)	Patients Without Cardiac Biopsy (n = 649)		Patients With Cardiac Biopsy (n = 104)	
	Total	ATTR-CA* (n = 127)	No Amyloidosis (n = 434)	ATTR-CA (n = 69)	No Amyloidosis (n = 22)
Age, yrs	76.7 ± 10.9	79.4 ± 8.4	76.8 ± 11.4	72.9 ± 8.5	69.9 ± 8.3
Male	513 (68)	96 (76)	264 (61)	59 (86)	17 (77)
Racial/ethnic background					
White	537 (71)	86 (68)	321 (74)	48 (70)	15 (68)
Black	106 (14)	22 (17)	58 (13)	10 (14)	5 (23)
Hispanic	49 (7)	5 (4)	27 (6)	5 (7)	1 (5)
Other/unknown	61 (8)	15 (12)	28 (6)	6 (9)	1 (5)
Echocardiography					
LV ejection fraction, % (n = 693)	55 (38-60)	47 (35-56)	55 (43-63)	46 (31-57)	50 (30-60)
IVS, mm (n = 736)	13 (11-15)	15 (13-18)	12 (10-13)	16 (15-19)	11 (10-14)
LVPWT, mm (n = 735)	12 (10-14)	15 (13-16)	11 (9-12)	16 (14-18)	10 (9-13)
Left atrial volume index, ml/m^2 (n = 556)	50 (40-63)	51 (43-62)	50 (39-65)	46 (41-52)	51 (46-78)
PYP visual score					
Grade 0	307 (41)	2* (1)	278 (64)	0 (0)	12 (55)
Grade 1	177 (24)	1* (1)	153 (35)	4 (6)	7 (32)
Grade 2	37 (5)	5 (3)	3 (1)	2 (3)	3 (14)
Grade 3	232 (31)	119 (94)	0 (0)	63 (91)	0 (0)
PYP H:CL (n = 751)					
<1.5	502 (67)	5 (4)	430 (100)	3 (4)	21 (95)
≥1.5	249 (33)	122 (96)	2 (0)	66 (96)	1 (5)

SPECT Results As Function Of Planar Visual Grading Score Patients Undergoing 99mtc-pyp Scanning

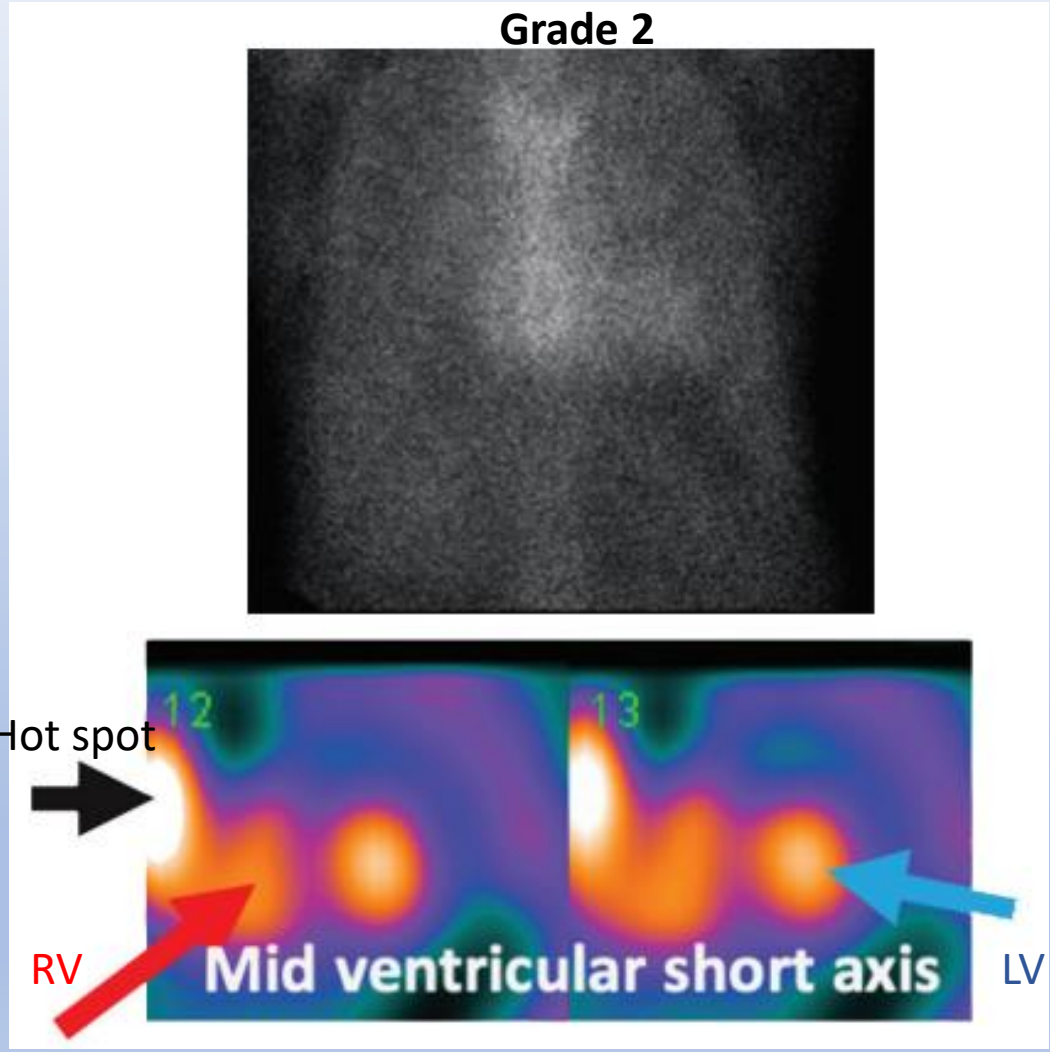




Grade	Planar visual score n=257 patients	SPECT + Myocardial uptake
0	72	0
1	81	0
2	25	9(36%)
3	79	79 (100%)

Diagnosing Transthyretin Cardiac Amyloidosis by Technetium Tc 99m Pyrophosphate

Poterucha et al .JACC: CARDIOVASCULAR IMAGING, VOL. 14, NO. 6, 2021



99mTc-PYP scanning that is visual score grade 2 with planar imaging alone is often a false positive result

Non-ATTR Causes of Positive Technetium-Labeled Cardiac Scintigraphy

False positive

- Blood pool
- Rib fractures that may overlay the heart, thereby raising radiotracer counts (affecting H/CL ratio calculation) or mimicking myocardial uptake.
- Acute or subacute myocardial infarction can lead to focal uptake.
- Rare forms of CA : hereditary apolipoprotein A1.

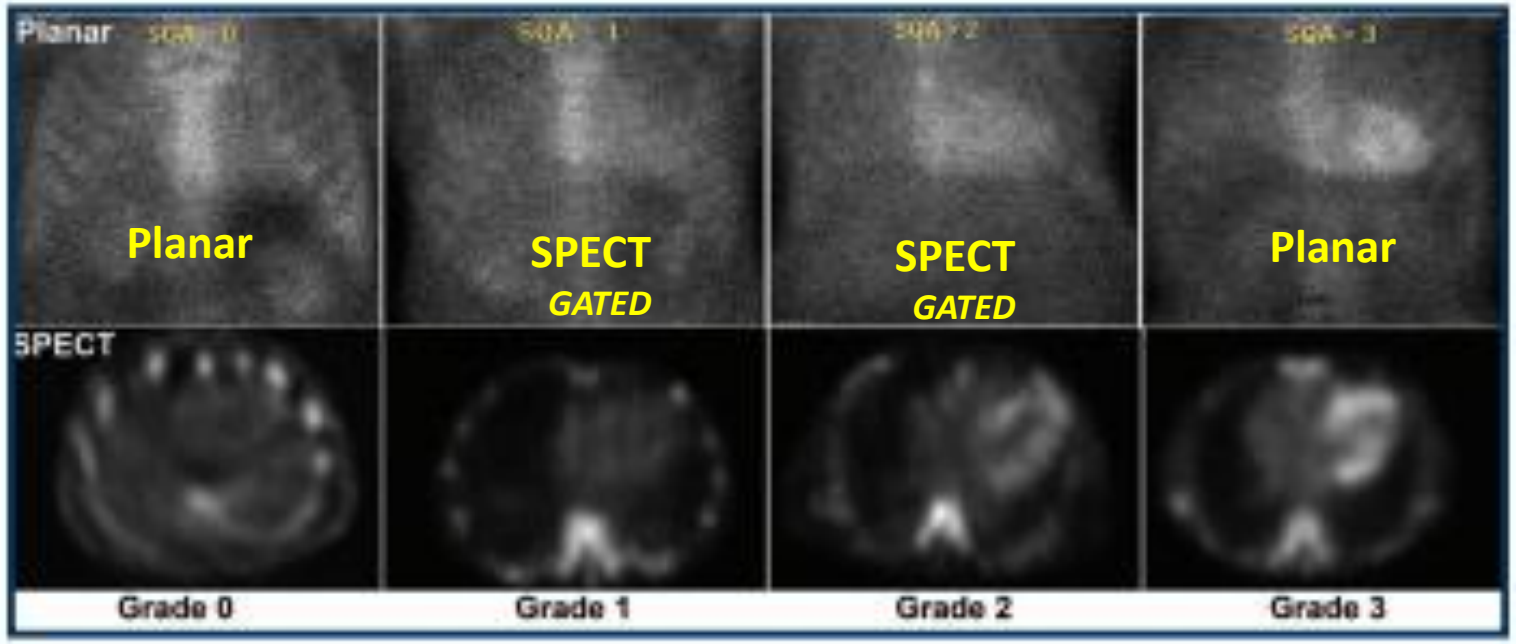
False negative

- TTR mutations: Phe64Leu and Val30Met, have been noted to have typical cardiac involvement by echocardiography but negative cardiac scintigraphy results.
- Myocardial infiltration is minimal, as in early stage disease, thus causing uptake to be below the current diagnostic detection threshold.
- Delayed or premature acquisition.

TTR Cardiac Amyloidosis ^{99m}Tc-PYP Imaging in 2022 Everyday Practice

Grading ^{99m}Tc-PYP Uptake on Planar an SPECT Images

Not suggestive ***Equivocal*** ***Strongly suggestive***



H/Cl ratio <1 **H/Cl ratio <1-1.5** **H/Cl ratio >1.5**

Early enthusiasm based upon data from highly selected referral populations is being tempered by the recognition of diminished accuracy that has been observed with widespread clinical application.

- As cardiac scintigraphy is increasingly used in screening populations with minimal increase in left ventricular wall thickness, we suspect that testing results are going to be less favorable with high false positive rates.

- Recognition that a single test alone does not establish or exclude the diagnosis of ATTR-CM is central to the proper application of 99mTc-PYP, 99mTcDPD, 99mTc-HMDP scintigraphy in the appropriate clinical context.

ATTR Cardiac Amyloidosis Imaging at the Present Time

- The combination of:

  careful case selection for cardiac scintigraphy,

  appropriate scanning protocols,

  confirmation of all positive planar imaging by SPECT,

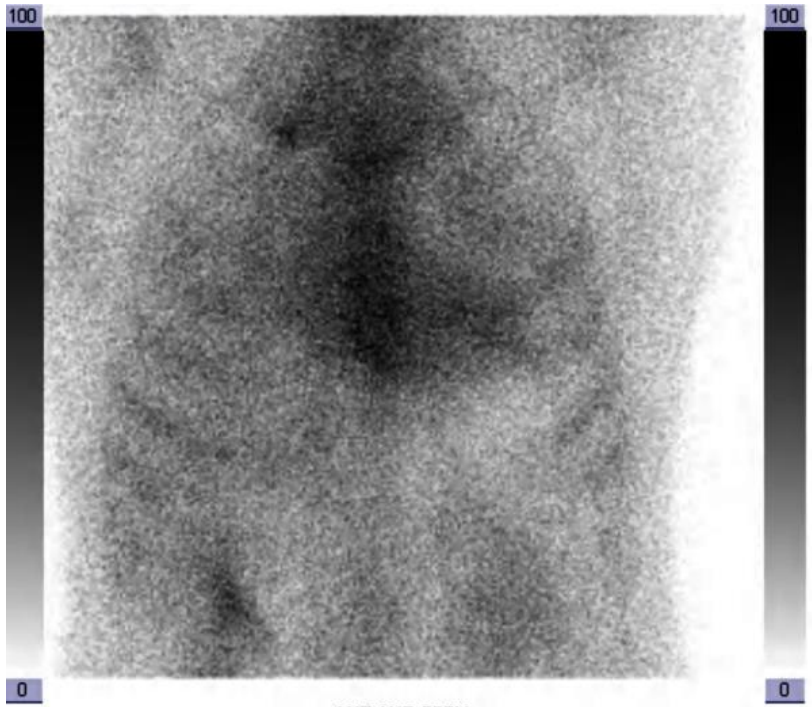
  may help to mitigate this and maintain diagnostic accuracy in the work-up of suspected ATTR-CA.

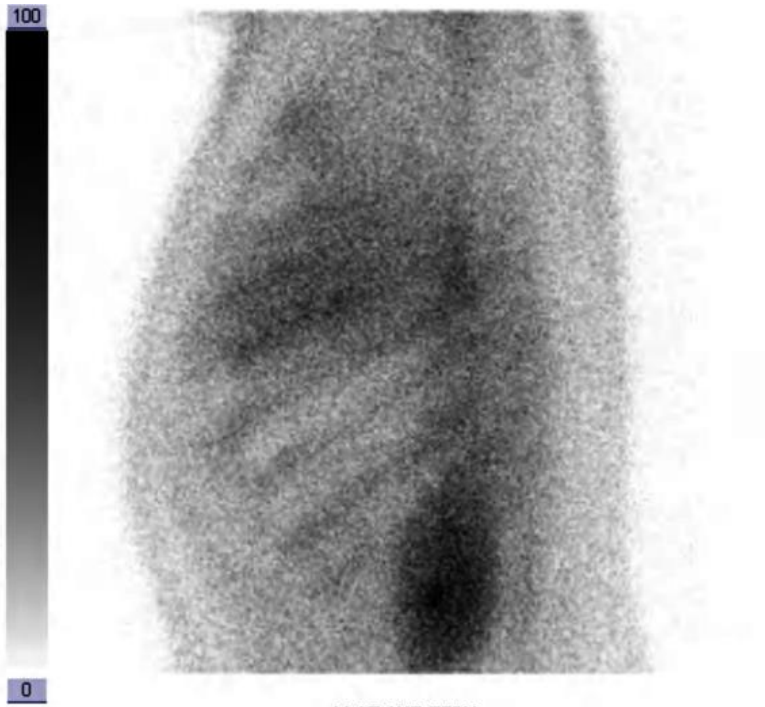
- Early and accurate diagnosis of ATTR cardiac amyloidosis makes possible targeted therapy with novel disease-modifying agents to substantially reduce heart failure hospitalization and improve survival.

KAPLAN MEDICAL CENTER
Your health-Our mission

Thank you for your attention

TTR Cardiac Amyloidosis Planar Imaging-PYP Tc-99m scan





Patient History:

Male, 60Y

NIDDM

HTN

CLBBB

Dilated CMP

True or false positive TTR-CA?

Where the uptake is?

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