Practical Applications for hATTR Amyloidosis Diagnosis

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Disclosures

Served on Advisory Board for Pfizer, Alnylam, Eidos, and Akcea Therapeutics in the past

THE OPINIONS EXPRESSED IN THIS PRESENTATION (AND/OR SLIDES) ARE SOLELY THOSE OF THE PRESENTER AND NOT NECESSARILY OF THE AMERICAN HEART ASSOCIATION / AMERICAN STROKE ASSOCIATION (AHA/ASA). THE AHA/ASA DOES NOT ENDORSE ANY SPECIFIC PRODUCTS OR DEVICES.

Objectives

Brief Review of Hereditary Transthyretin Amyloidosis

Basic Algorithm to Diagnose Hereditary Transthyretin Amyloidosis

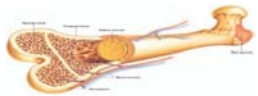
Review Common Misdiagnoses

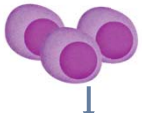
Case Examples in Diagnosis and Management

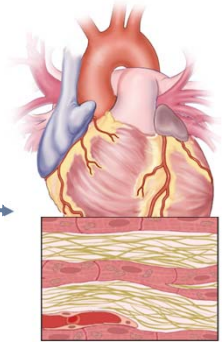
Two Main Types of Amyloidosis That Affect the Heart

AL

Light chain amyloidosis



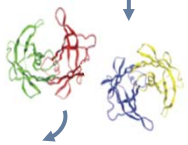




ATTR

Transthyretin amyloidosis

Wild Type
Hereditary



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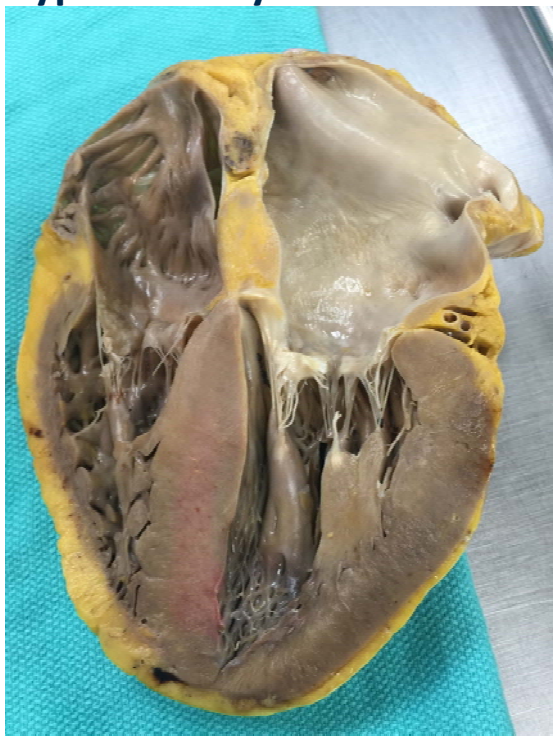
Two Main Types of Amyloidosis That Affect the Heart



Transthyretin (ATTR) Amyloidosis

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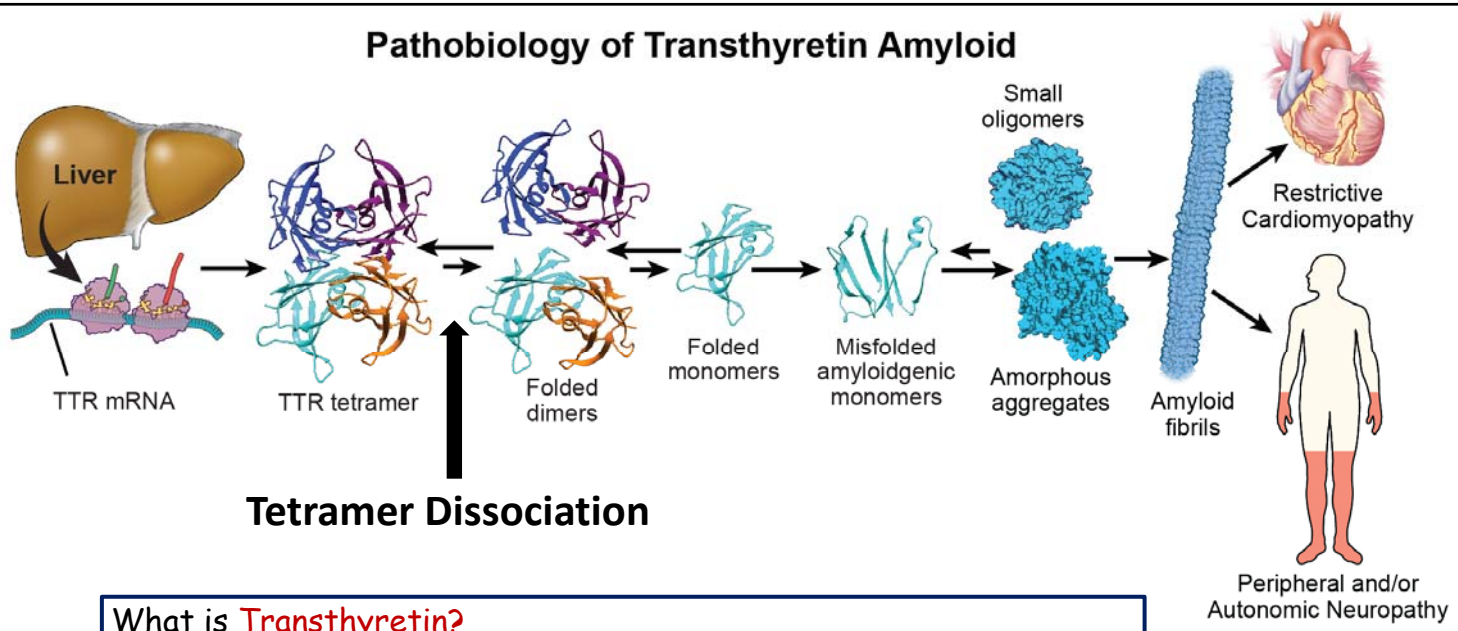

What is Transthyretin?

Transport protein for Thyroxine and Retinol binding protein
Homotetramer made up of 4 identical monomers (127 a.a)
Used be called “Prealbumin”, still see this name on our labs

Transthyretin Amyloidosis (ATTR)

Wild Type (ATTRwt)

- No mutation in TTR gene
- Not hereditary
- Median age at dx 74 years
- 25% of pts > 85 yrs have ATTRwt on autopsy

Variant (ATTRv)

- Mutation in TTR gene present
- It's hereditary
- Age depends on specific mutation
- Most common in US is V122I
  - Late onset cardiac amyloid

- Carpal Tunnel Syndrome
- Spinal Stenosis causing back pain
- Biceps Tendon Rupture (wild type)
- Shoulder pathology
- Hip/Shoulder/Knee surgeries

Hanna M, Curr Heart Fail Rep 2014, Mar;11(1):50-7

TTR Genetic Testing

- Short gene on chromosome 18
- Simple test of the blood or saliva
- Turn around 2-3 weeks
- Involve genetic counselors

Presentation

CARDIAC

- Heart Failure (HFpEF, HFmrEF, HFrEF)
- Atrial fibrillation / cardioembolic stroke
- "Hypertrophic cardiomyopathy"
- Low flow low gradient aortic stenosis
- Pacemaker / Complete heartblock
- Angina w normal cors

NON-CARDIAC

- Autonomic Neuropathy
  - Diarrhea
  - Orthostatic hypotension
  - Erectile dysfunction
- Peripheral Neuropathy
- Vitreous Opacities (7 mutations)
- Bilateral carpal tunnel / Spinal Stenosis
- Nephrotic Syndrome (V30M)

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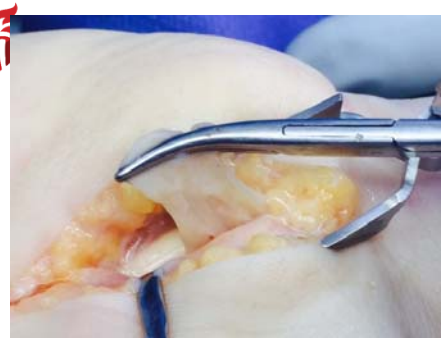
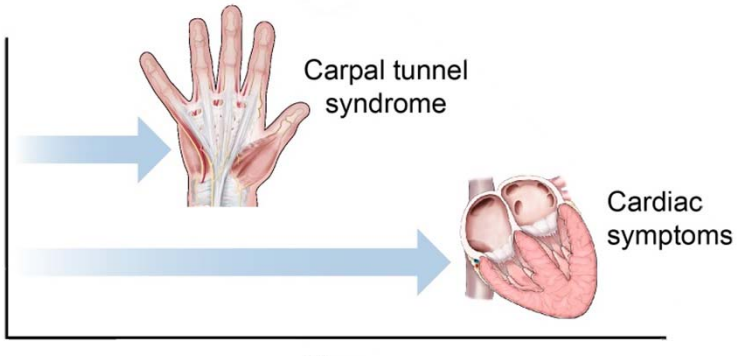
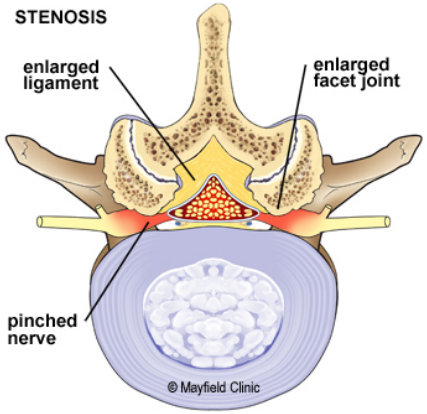
Ask these questions in pts with Heart Failure and increased wall thickness

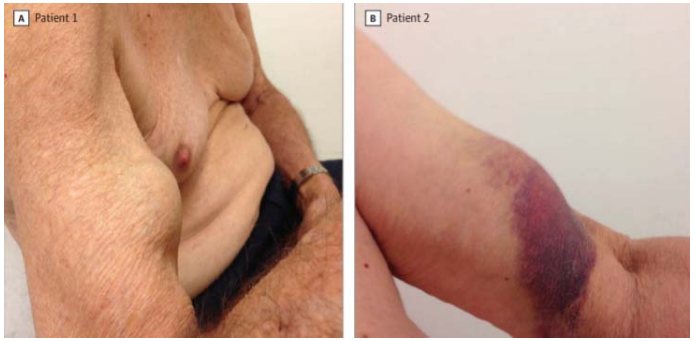
1. Carpal Tunnel syndrome, bilateral
2. Spinal Stenosis
3. Biceps tendon rupture
4. Shoulder pathology: rotator cuff

Sperry, B, J Am Coll Cardiol. 2018 Oct 23;72(17):2040-2050 Geller, HI, JAMA. 2017 Sep 12;318(10):962-963









Sperry, B, J Am Coll Cardiol. 2018 Oct 23;72(17):2040-2050 Geller, HI, JAMA. 2017 Sep 12;318(10):962-963

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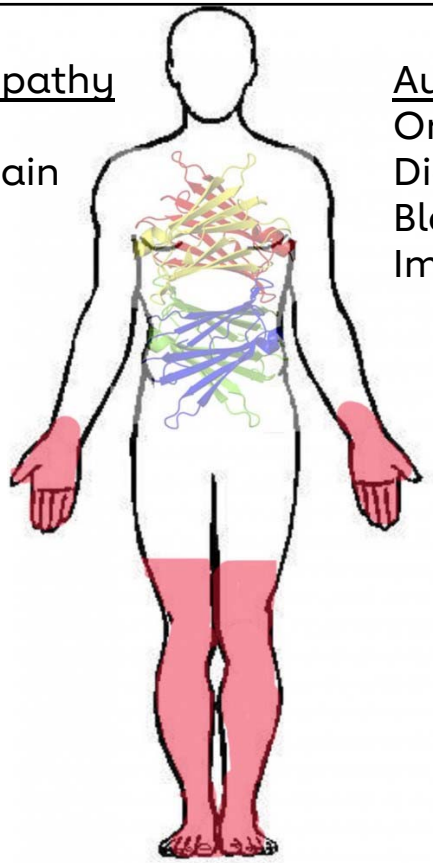
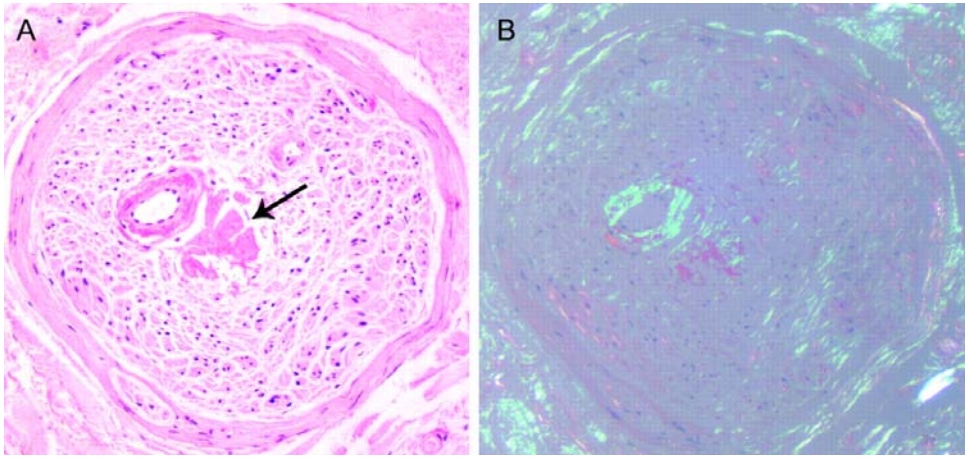
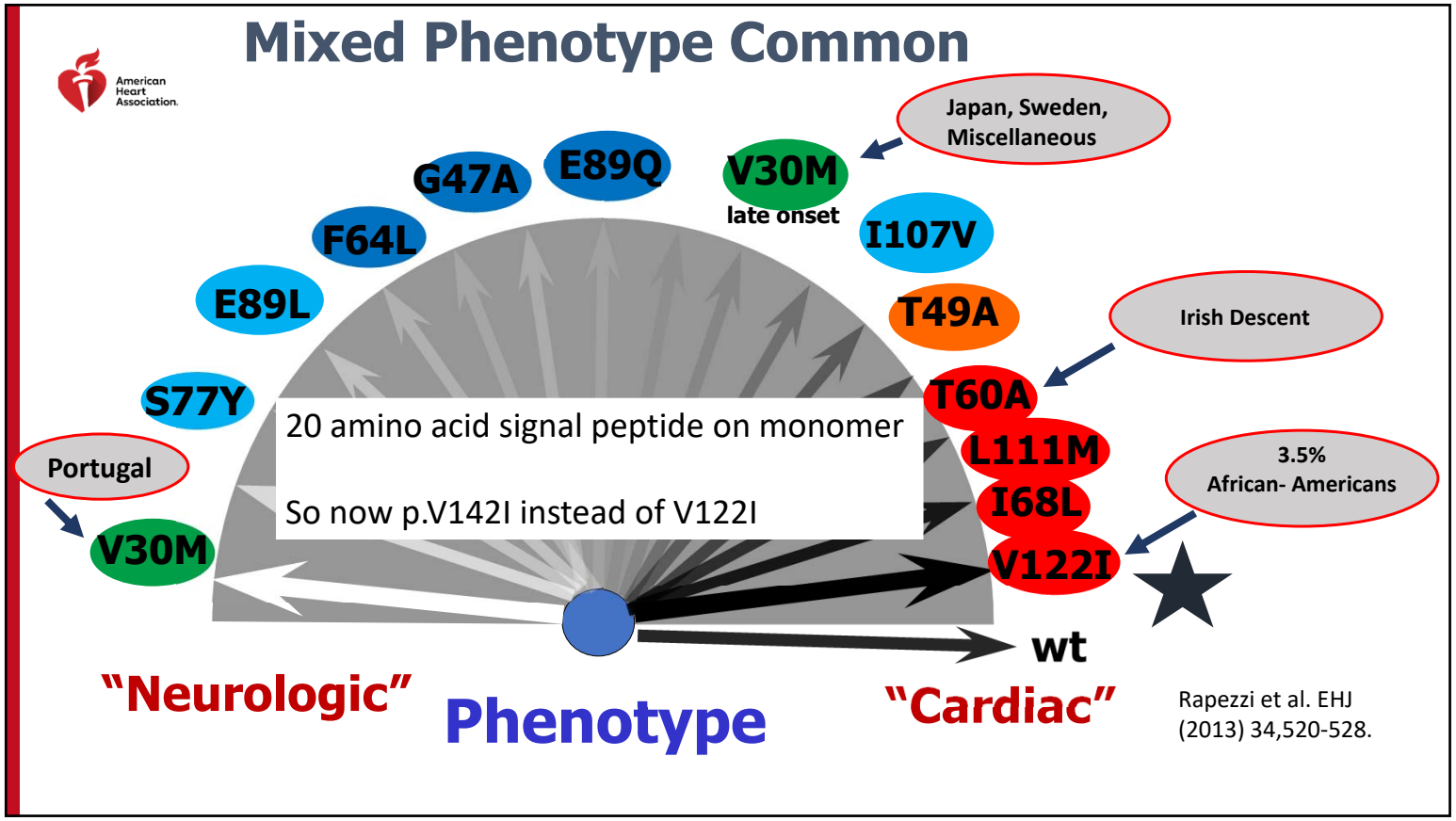
Peripheral Neuropathy
Sensory-Motor
Numbness and Pain
Weakness



Autonomic Neuropathy
Orthostatic hypotension
Diarrhea
Bladder
Impotence


A
B

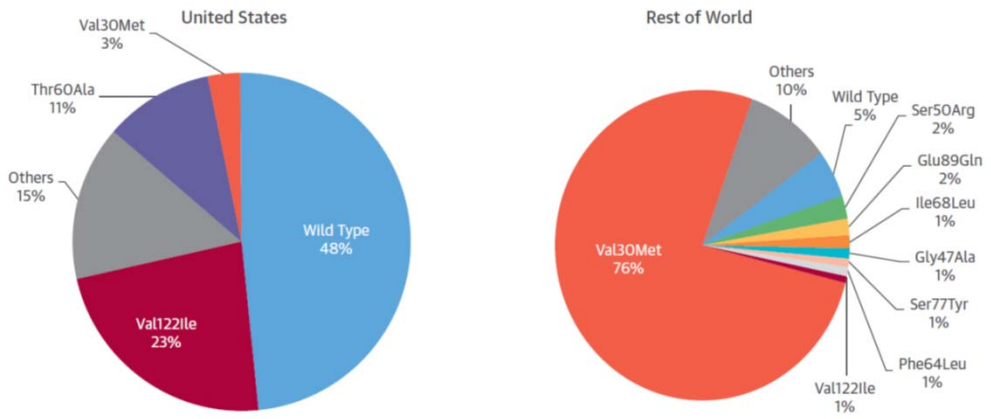
- Diabetic Neuropathy
- Idiopathic Neuropathy
- CIDP (chronic inflammatory demyelinating polyneuropathy)
- Alcoholic/Toxic (chemo, etc)
- Paraneoplastic Neuropathy
- Carpal Tunnel Syndrome
- ALS
- Motor Polyradiculoneuropathy
- AL Amyloidosis


Mixed Phenotype Common
American Heart Association.
Japan, Sweden, Miscellaneous
V30M
late onset
G47A
E89Q
F64L
I107V
E89L
T49A
Irish Descent
S77Y
T60A
20 amino acid signal peptide on monomer
So now p.V142I instead of V122I
L111M
Portugal
I68L
3.5% African- Americans
V30M
V122I
wt
"Neurologic"
Phenotype
"Cardiac"
Rapezzi et al. EHJ (2013) 34,520-528.

Genotype and Phenotype of Transthyretin Cardiac Amyloidosis

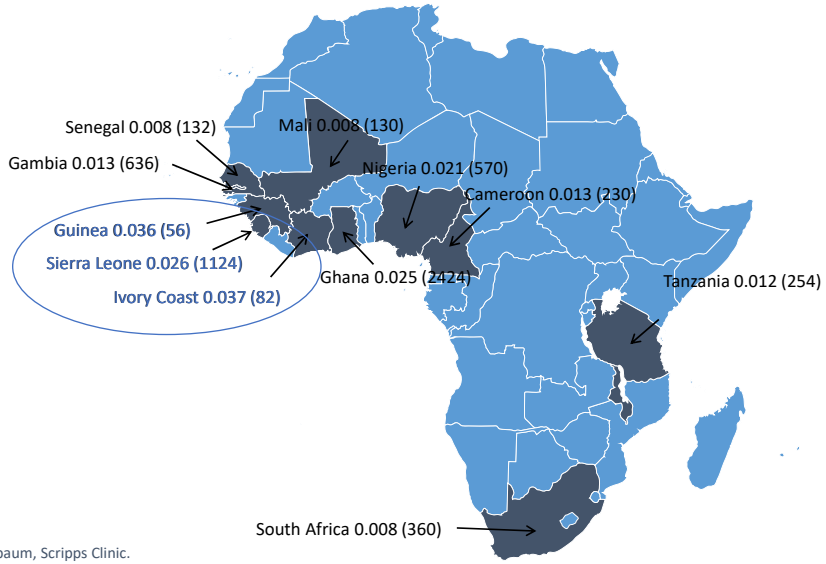
THAOS (Transthyretin Amyloid Outcome Survey)

FIGURE 2 Distribution of Mutations



Maurer et al. JACC 2016

Transthyretin V122I Allele Frequencies in Africa



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Courtesy of Joel Buxbaum, Scripps Clinic.
Jacobson DR, et al. *Mol Genet Genomic Med*. 2016;4(5):548–556.

V122I (p.V142I)

- First described in 1988 in an African-American man
- Unique – predominantly in patients with African descent
- Age-dependent autosomal dominant, median age 68-70 yrs
- Males 70%, female 30%
- Median survival worse than wild type (2.5 years)
- Prevalence of ~3.5% of African Americans (44 million in US)
  - ~ 1.5 Million carriers*
  - ~200,000 aged ≥65 years*

*Estimation based on US Census.

Gorevic et. al, J Clin Invest. 1989;83(3):836-843

Connors et. al, American Heart Journal 2009; 158(4): 607-614

Kittleson et. al, Circulation 2020; 142: e7-e22

Ruberg et. al, Circulation 2012; 126: 1286-1300

U.S. Census Bureau

T60A (pT80A) ("Ala60")

Mixed phenotype

Cardiomyopathy
- -Severe LV thickening, HF
- -high rates heart block

Neuropathy
- -Sensory-Motor
- -Autonomic (can be severe)

DONEGAL, IRELAND

Hewitt et. al, Journal of Cardiac Failure 2020; 26(10): 533

American Heart Association.

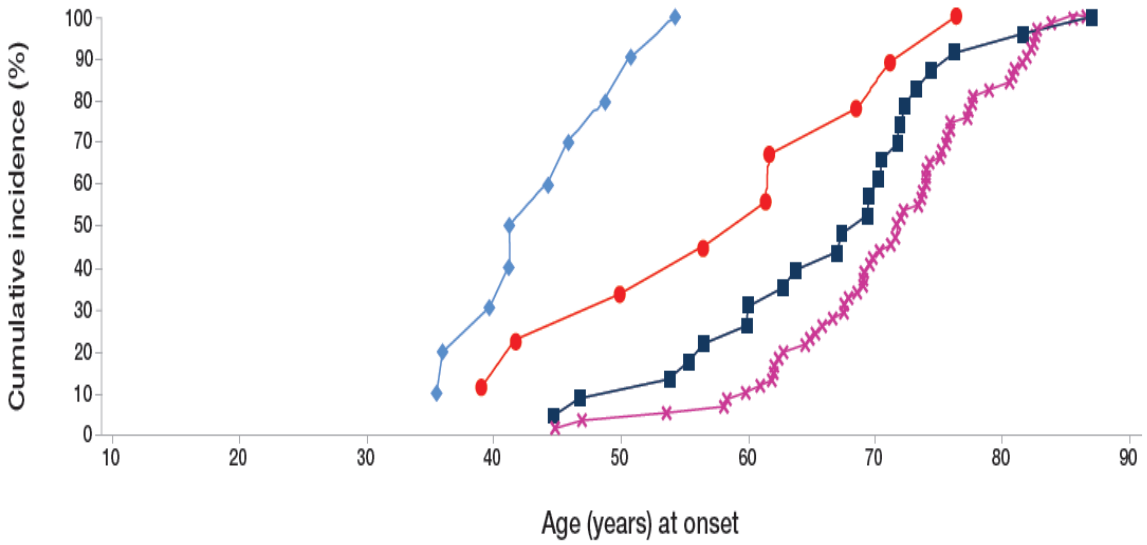
Table 1. Characteristics of Wild-Type and Common Variant Transthyretin Cardiac Amyloidosis

Mutation	Origin	Prevalence	Male:Female Ratio	Onset	Organs
SSA	Worldwide	25% >85 y	25:1 to 50:1	>60 y	Heart, ST
V122I	United States, Caribbean, Africa	4% Black	1:1 Gene (+) 3:1 Disease	>65 y	Heart, PNS, ST
V30M	Portugal, Sweden, Japan	1:1000	2:1	>50 y	PN/ANS, heart
T60A	United Kingdom, Ireland	1% Northwest Ireland	2:1	>45 y	Heart, PNS/ANS

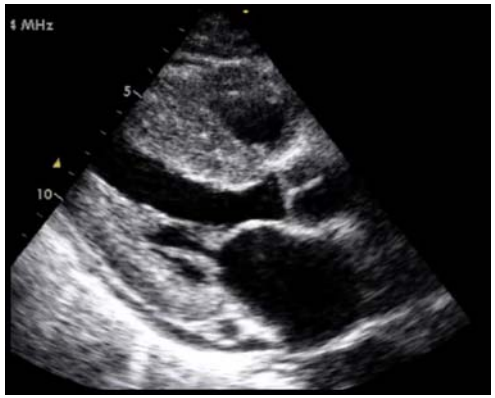
SSA indicates senile systemic amyloidosis, wild-type (no mutation); ST, soft tissue; PNS, peripheral nervous system; and ANS, autonomic nervous system.

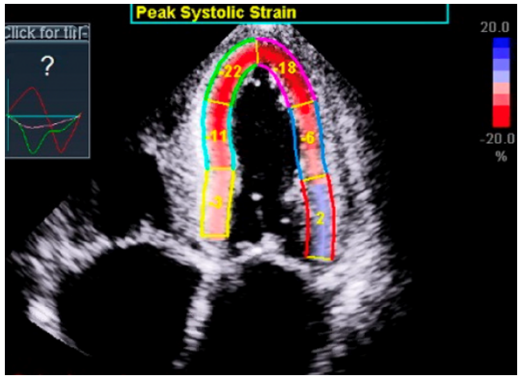
Ruberg et. al, Circulation 2012; 126: 1286-1300

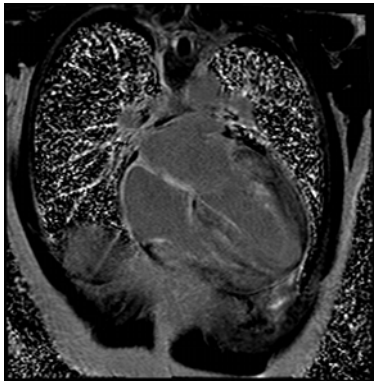
Age Dependent Penetrance

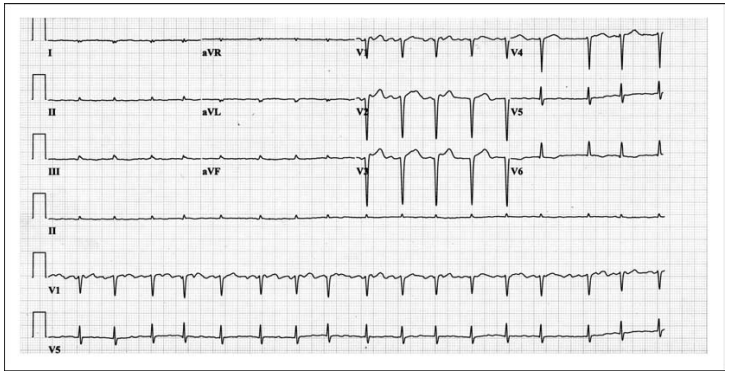


THAOS Registry









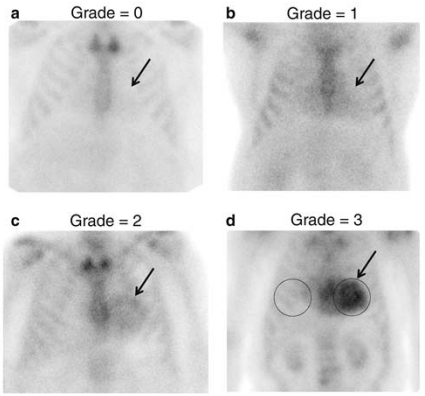
Important Points

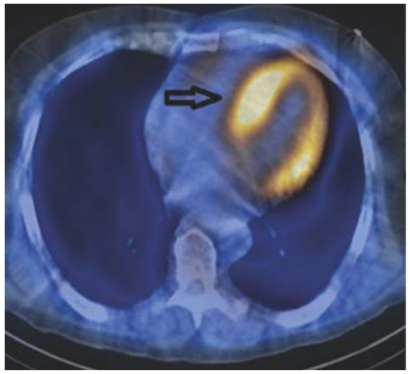
Classic low voltage only about 30% in ATTR-CM, 50% AL

LVH criteria seen in about 10% of biopsy proven CA

Discordance between ECG voltage and LV wall thickness

Conduction disease common
- PR interval increase
- IVCD, RBBB, LBBB
- Left axis deviation





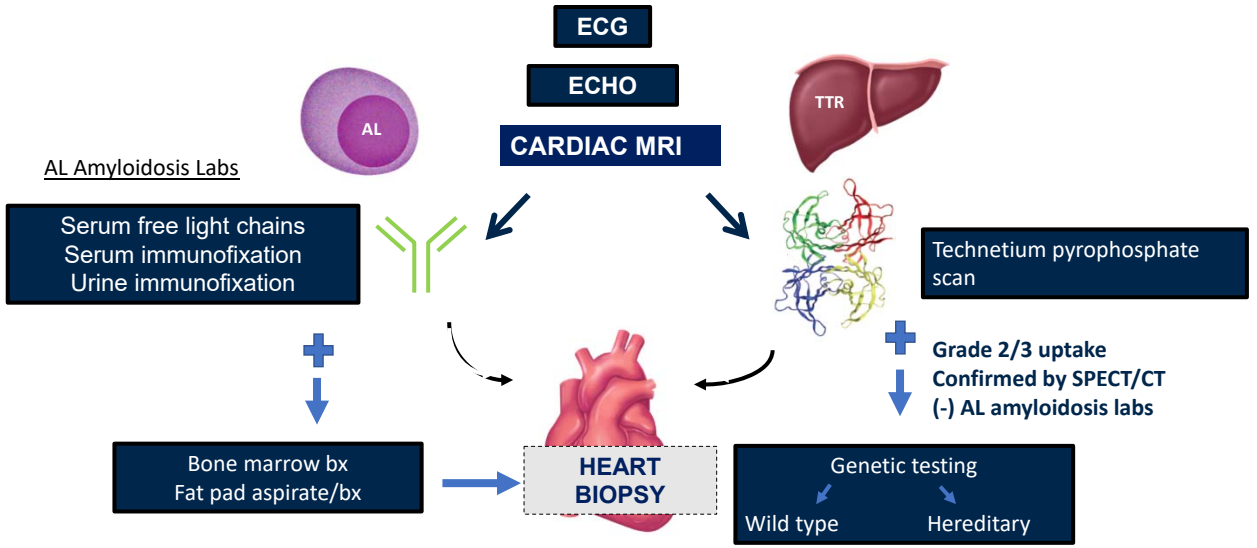
Lab Testing for AL Amyloidosis

Serum free light chain assay (kappa/lambda)
Serum immunofixation (SIFE)
Urine immunofixation (UFIE)

Chen et. al, Current Cardiology Reports 2018

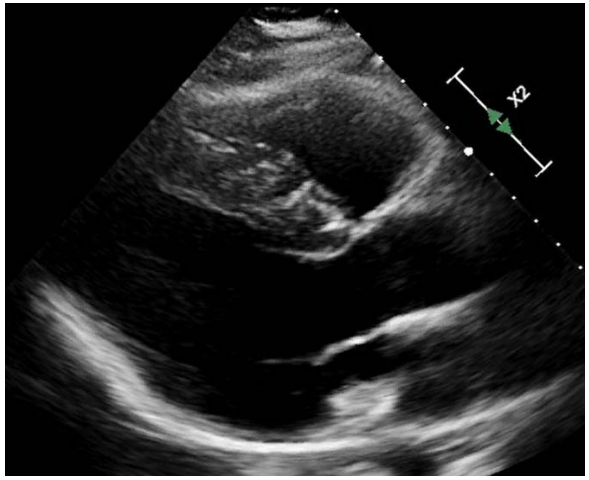
Banypersad et. al, Journal of the American Heart Association 2012

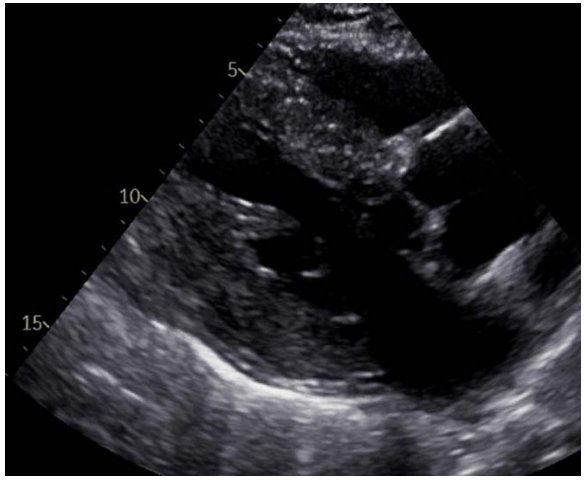
Starts With Clinical Suspicion

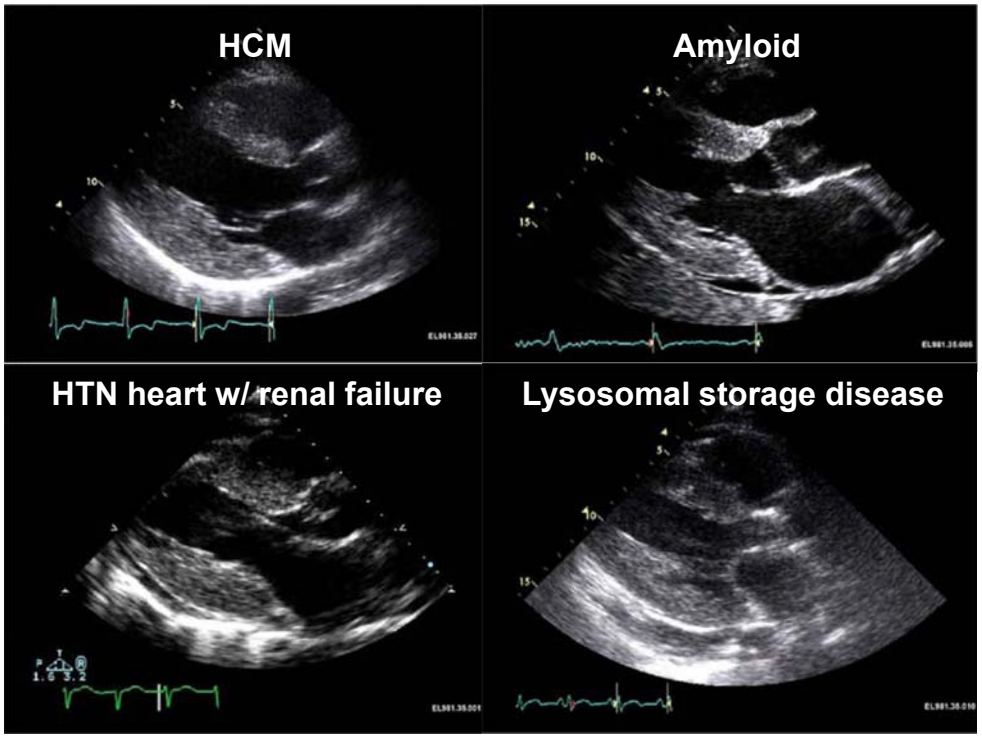


Hypertension versus Cardiac Amyloidosis?

THEY CAN COEXIST!!



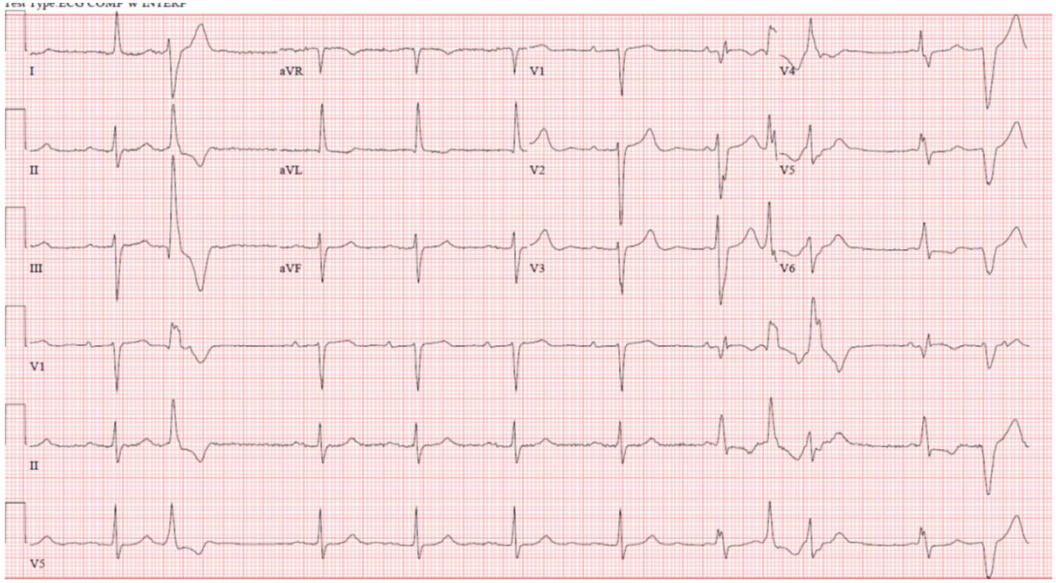



HCM
Amyloid
HTN heart w/ renal failure
Lysosomal storage disease

American Heart Association.

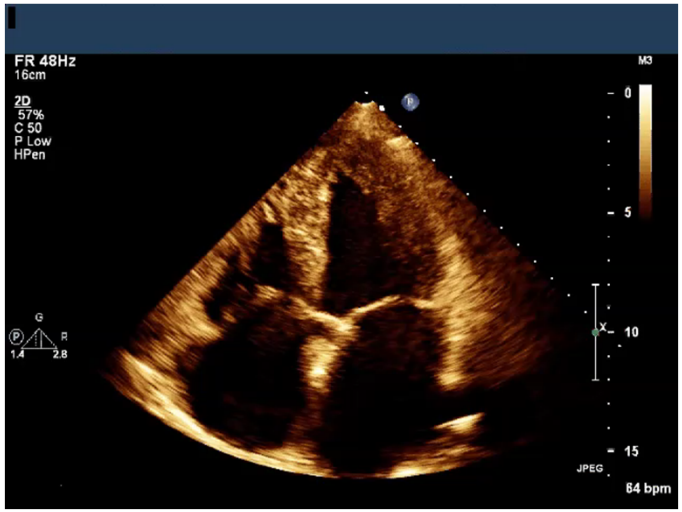
Case Examples

78 yo AA female h/o HTN & EF 45%
Referred for shortness of breath

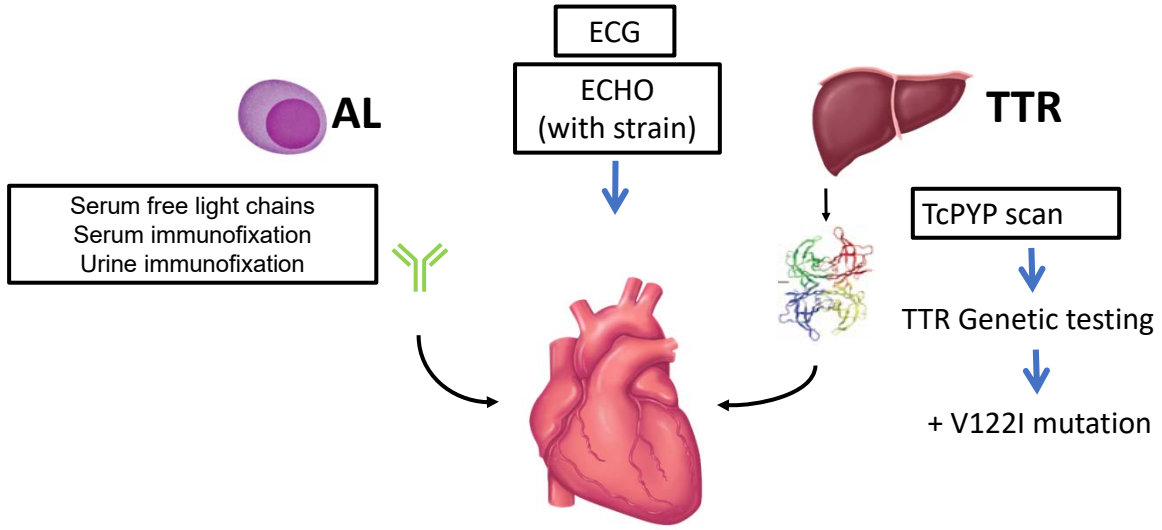


Echocardiogram

@maz_hanna



Diagnostic Work Up



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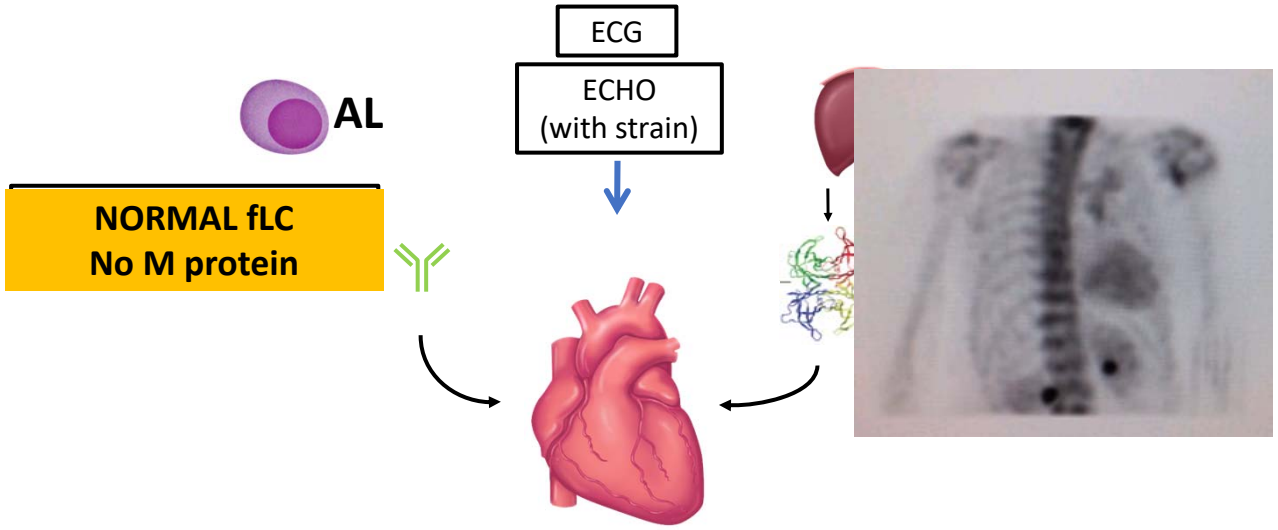

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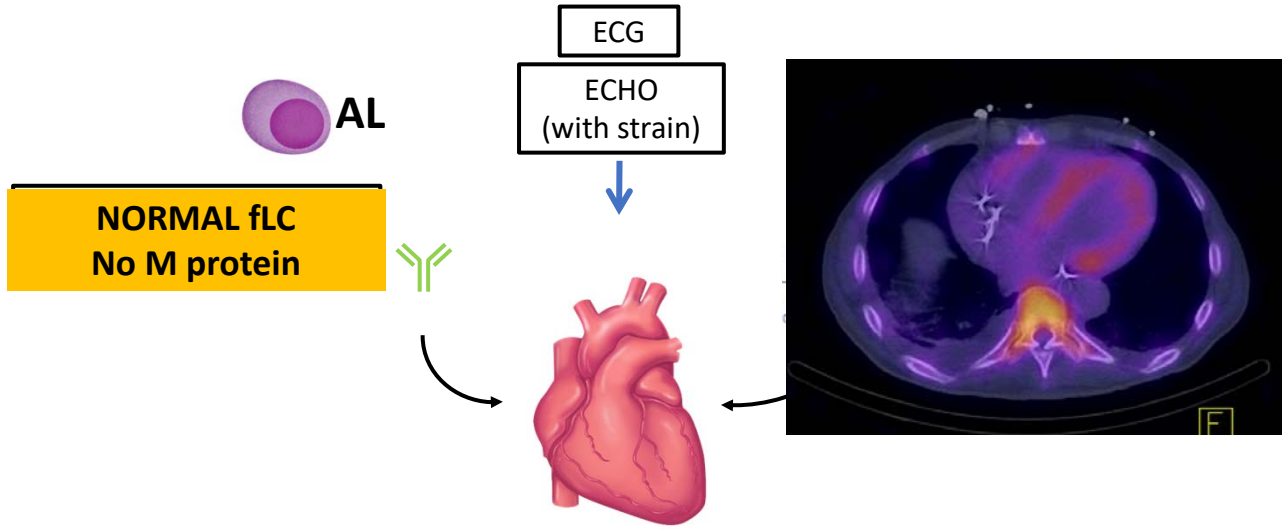

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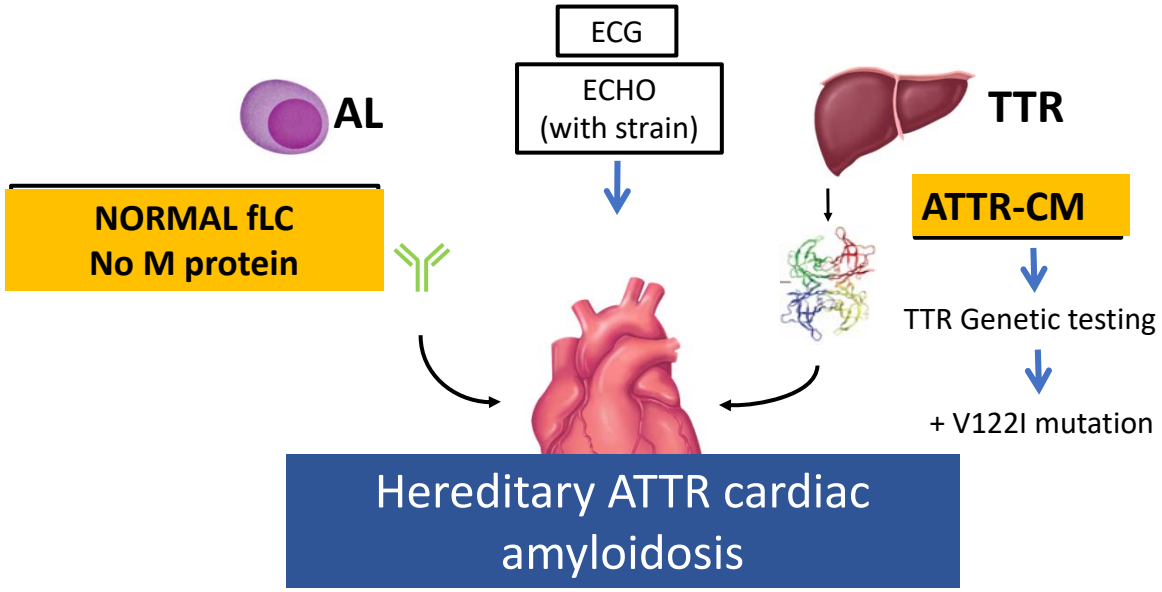
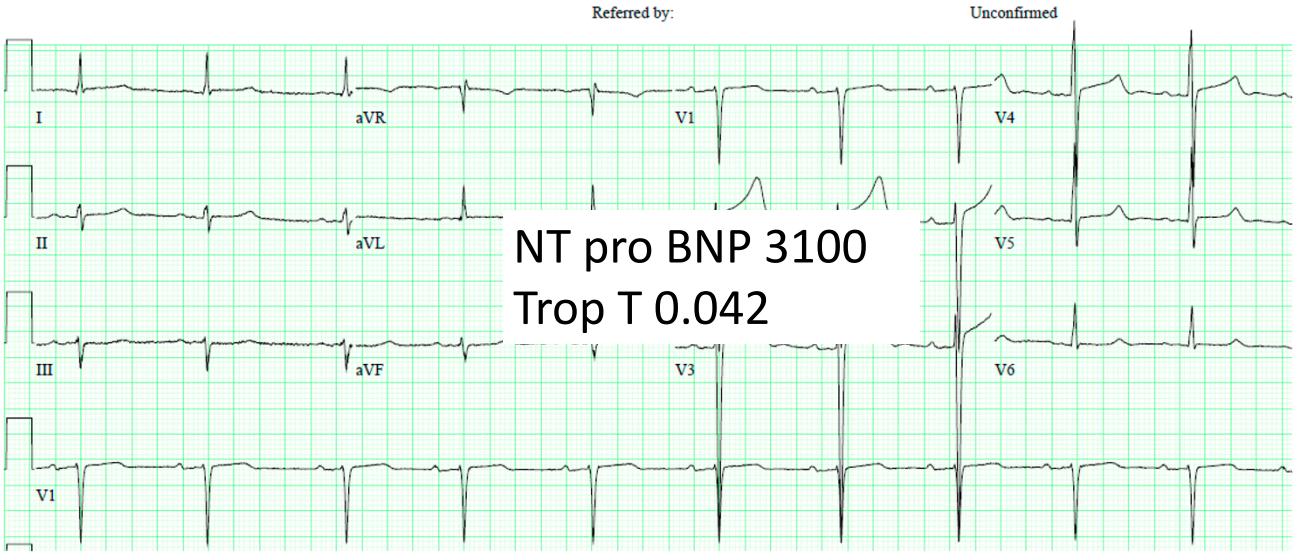


73 yo AA male h/o Kappa MGUS



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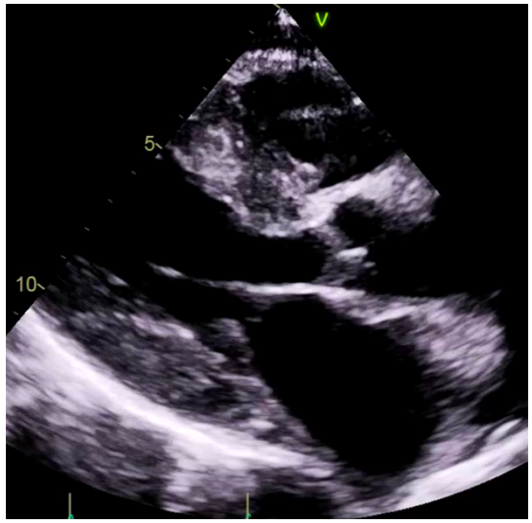
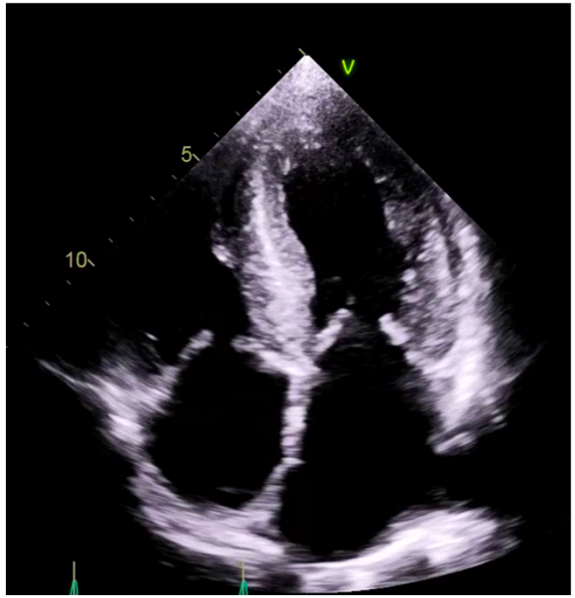
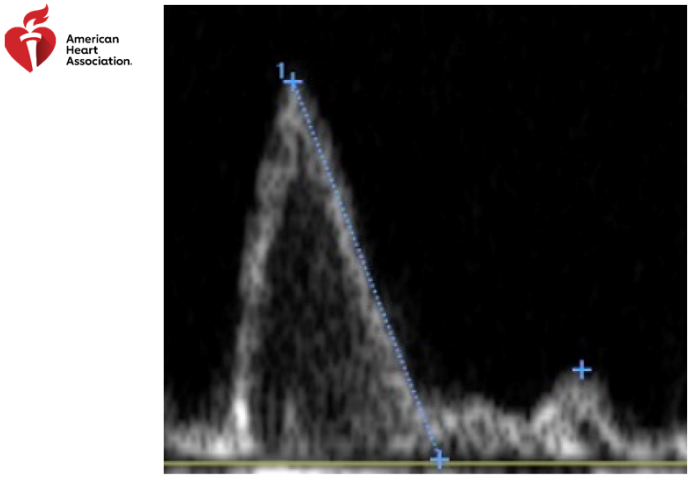
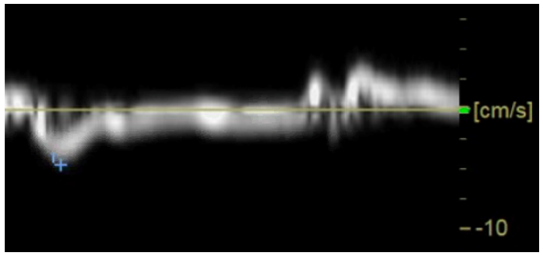
American Heart Association.





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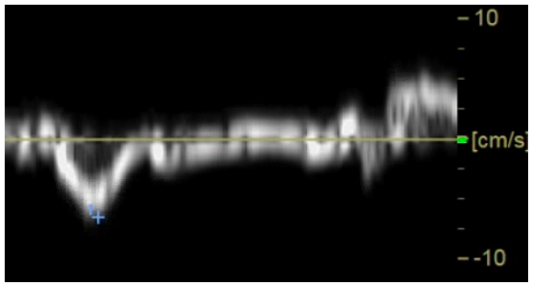
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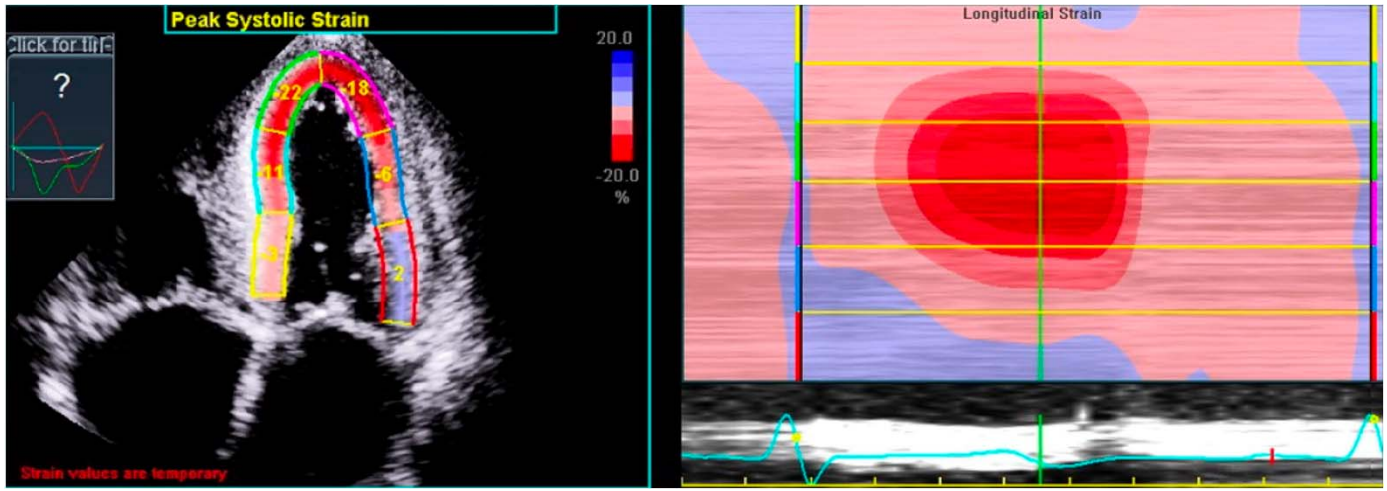
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Click for tiff
?
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-18
-11
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-2
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-20.0
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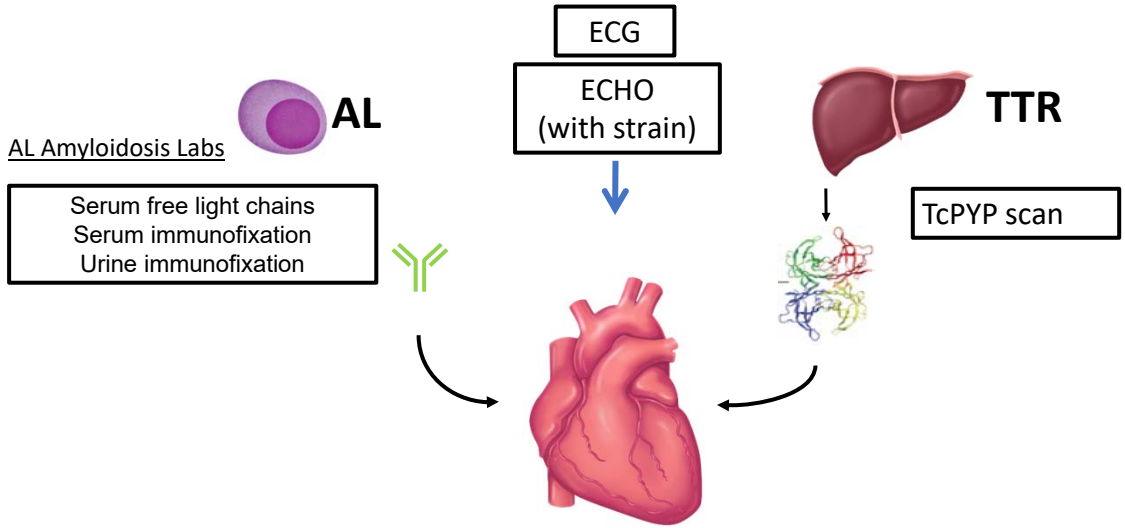
Strain values are temporary
Longitudinal Strain

Diagnostic Work Up



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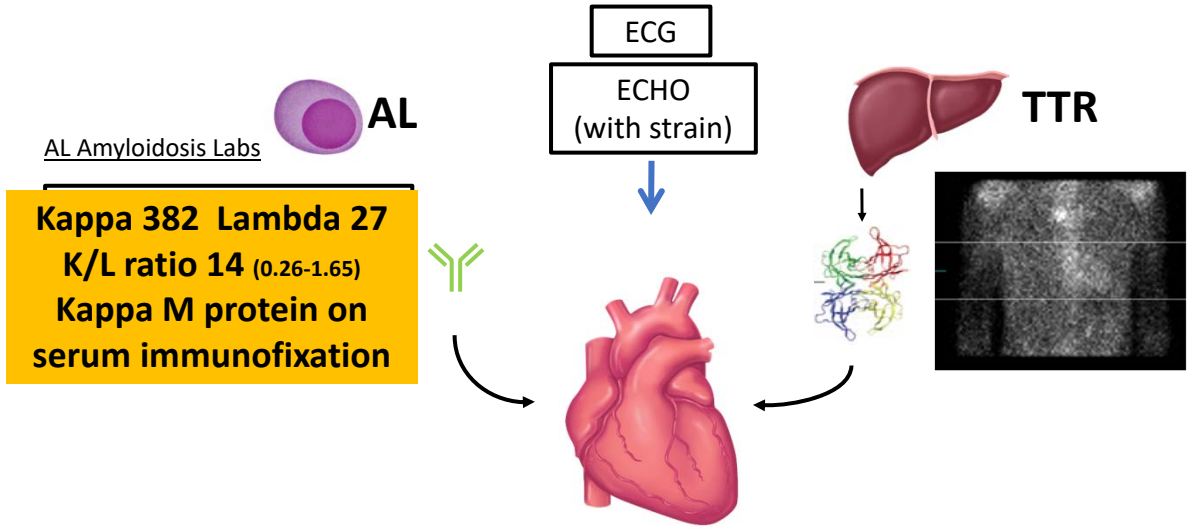

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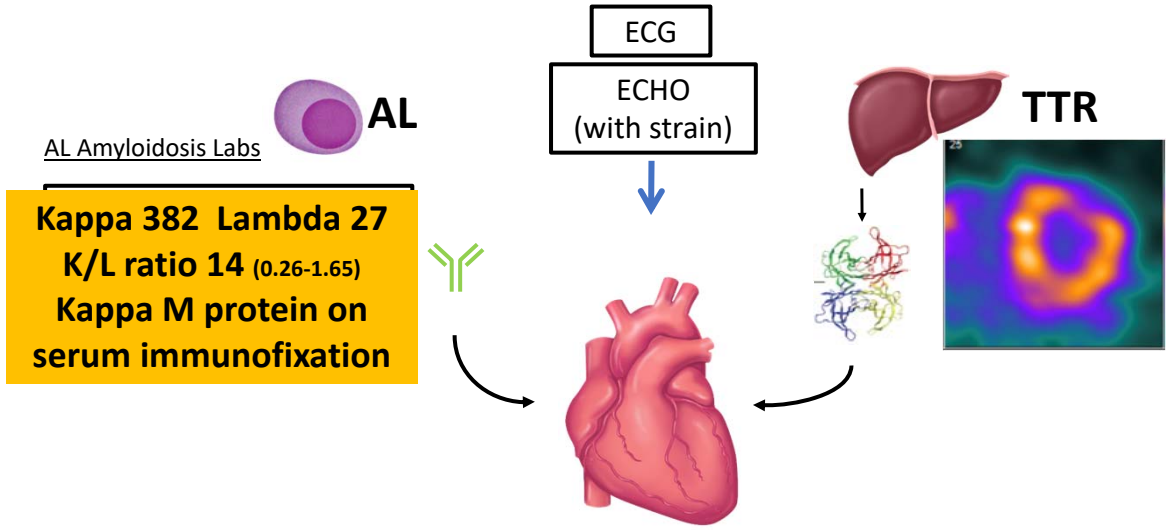

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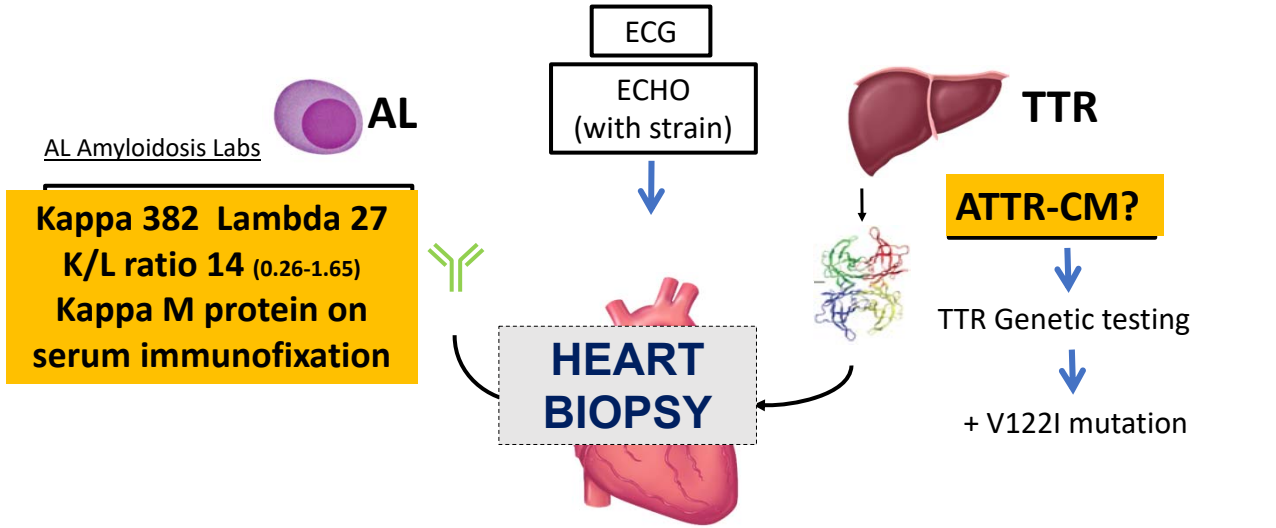
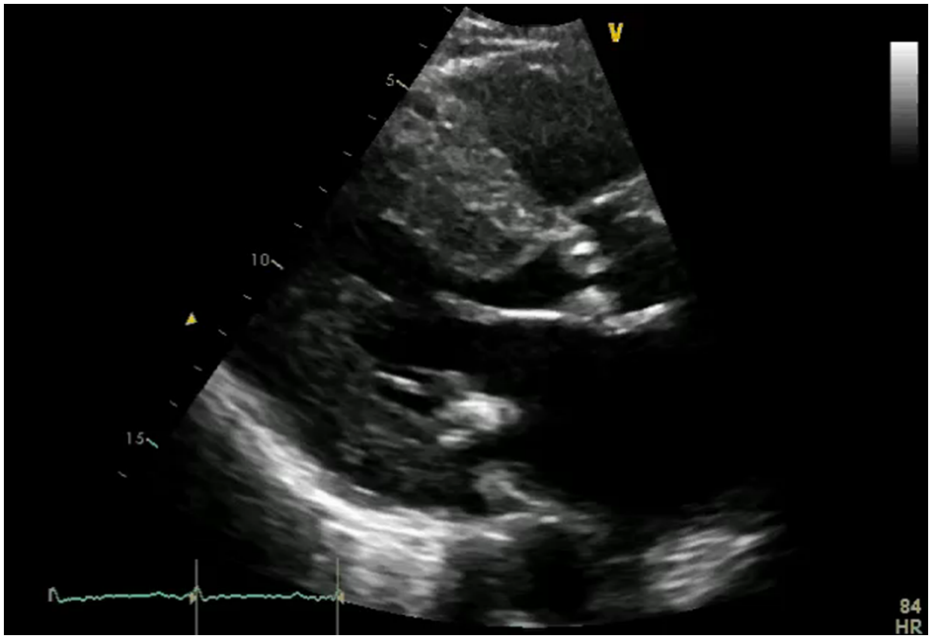
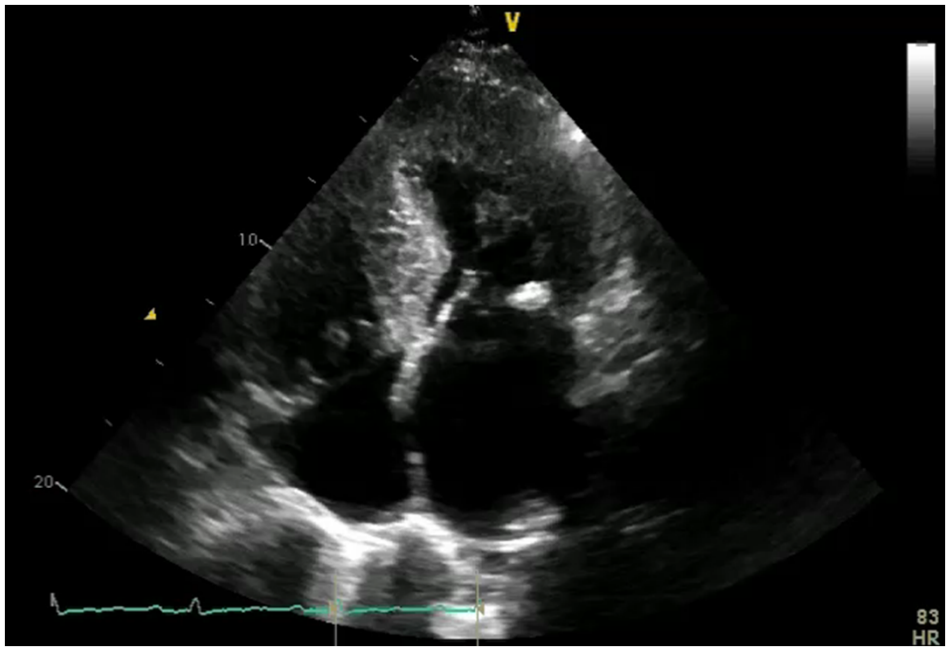


Hereditary ATTR amyloidosis + Kappa MGUS

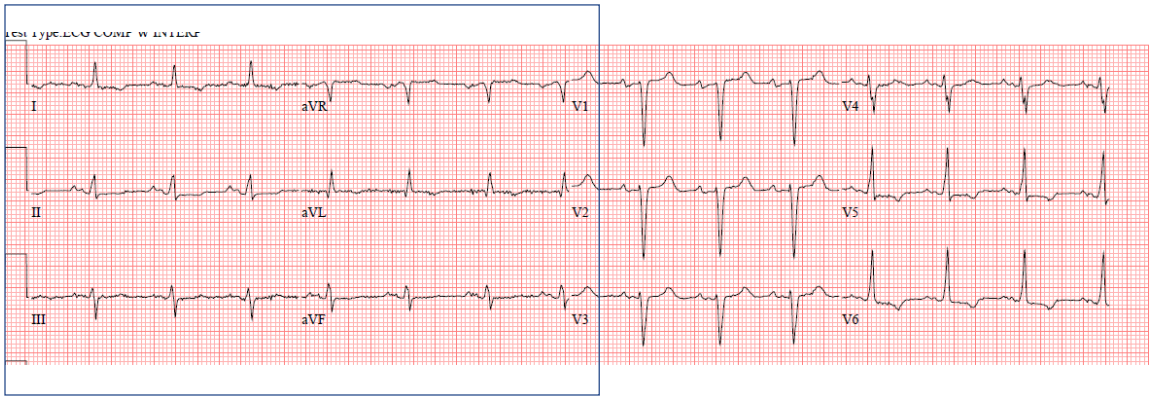
77 yr old AA female w/ CHF and aortic stenosis



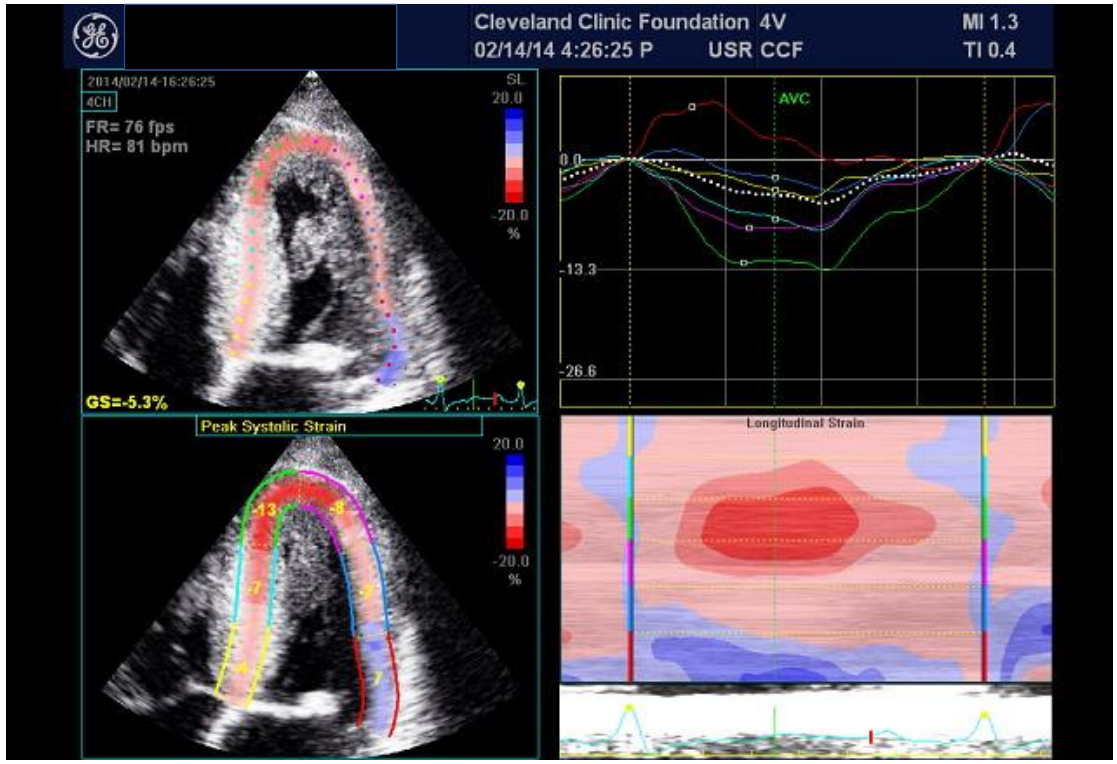
Severe concentric thickening of the LV

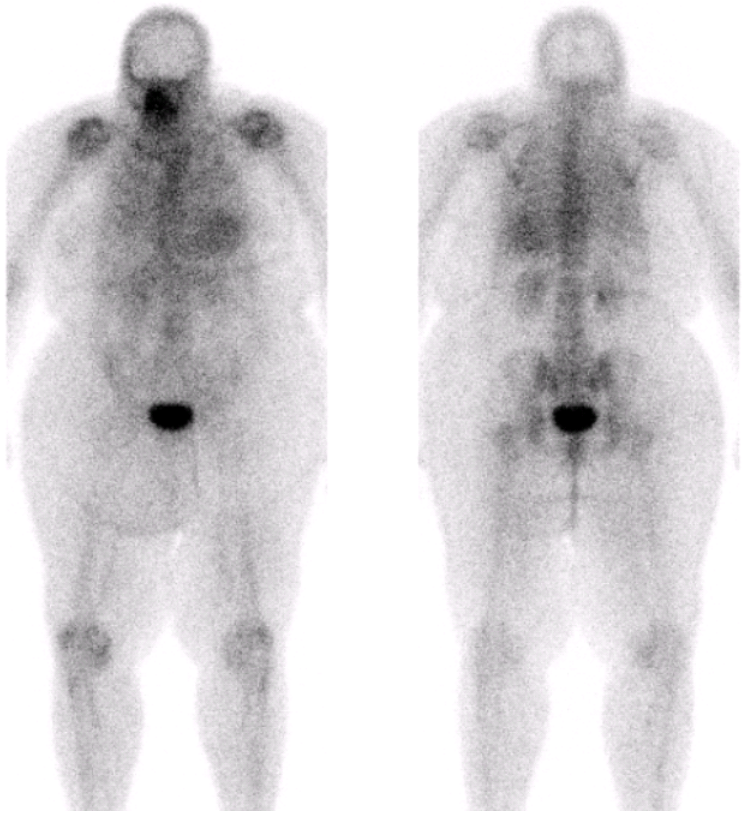


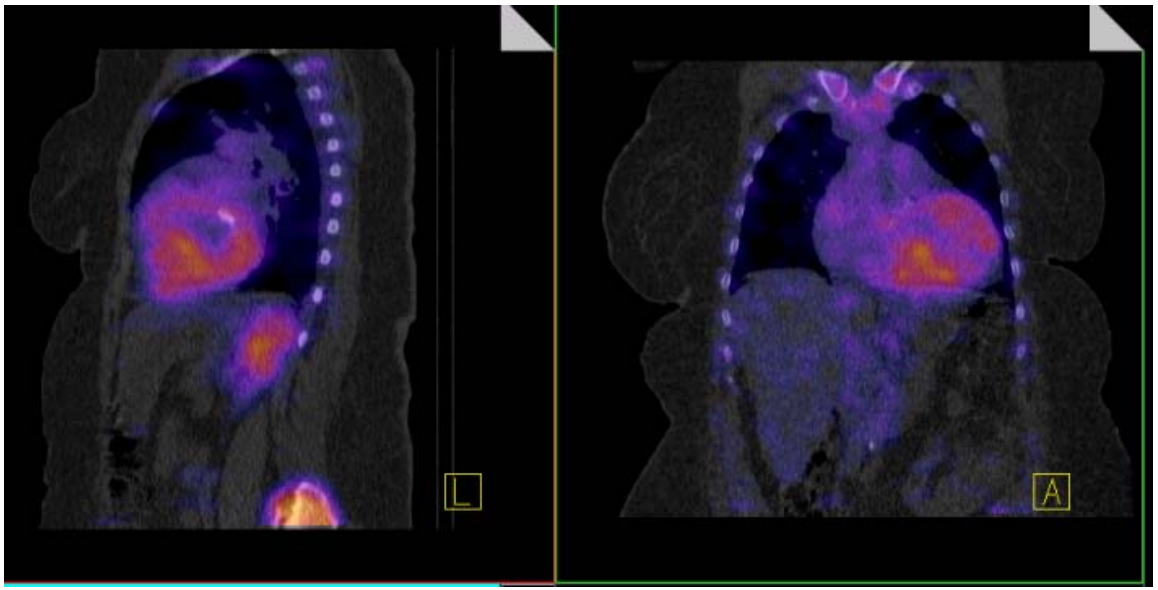
12-lead ECG



AND..... → 78 yr old African American ♀

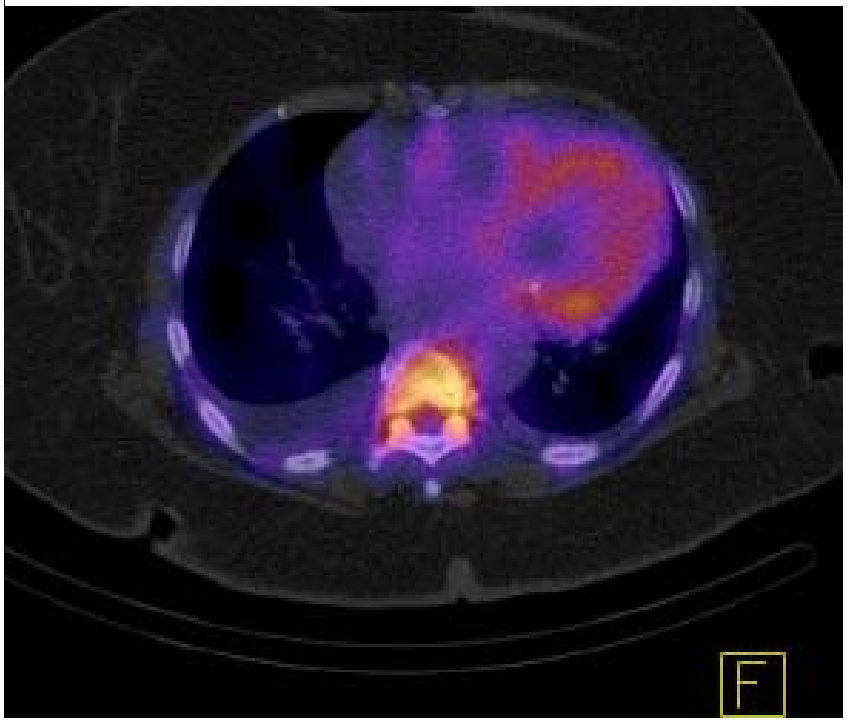

Cleveland Clinic Foundation 4V
02/14/14 4:26:25 P USR CCF
MI 1.3
TI 0.4
2014/02/14-16:26:25
4CH
FR= 76 fps
HR= 81 bpm
SL
20.0
-20.0
%
GS=-5.3%
Peak Systolic Strain
AVC
0.0
-13.3
-26.6
Longitudinal Strain




L
A

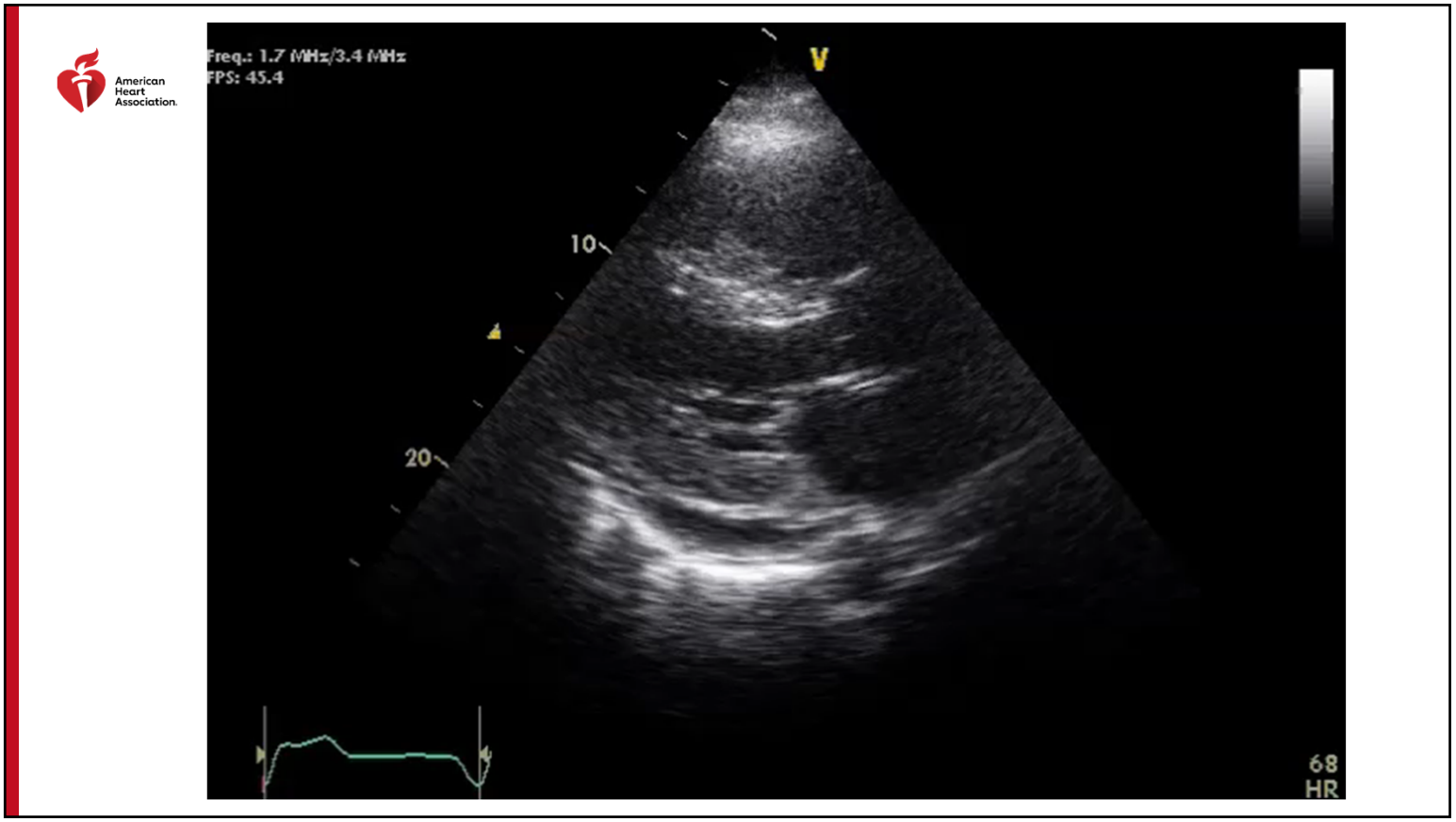
American Heart Association.

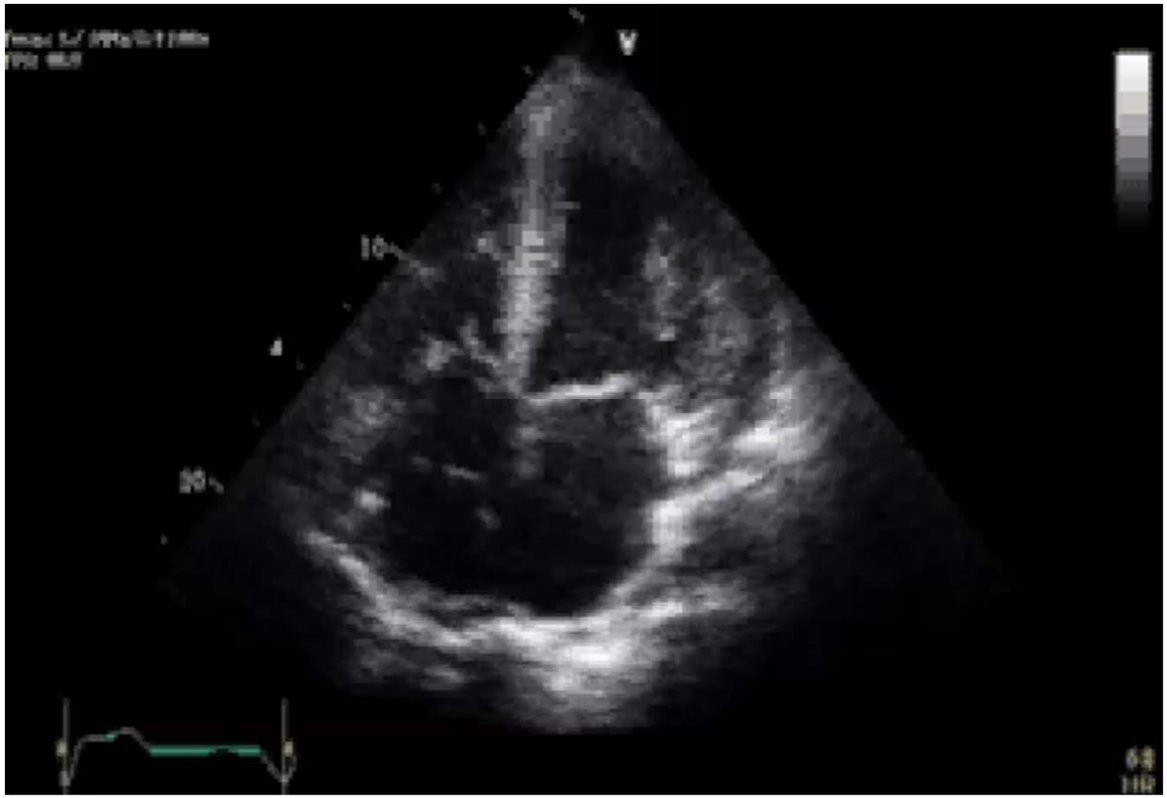
Genetic testing positive for V122I mutation

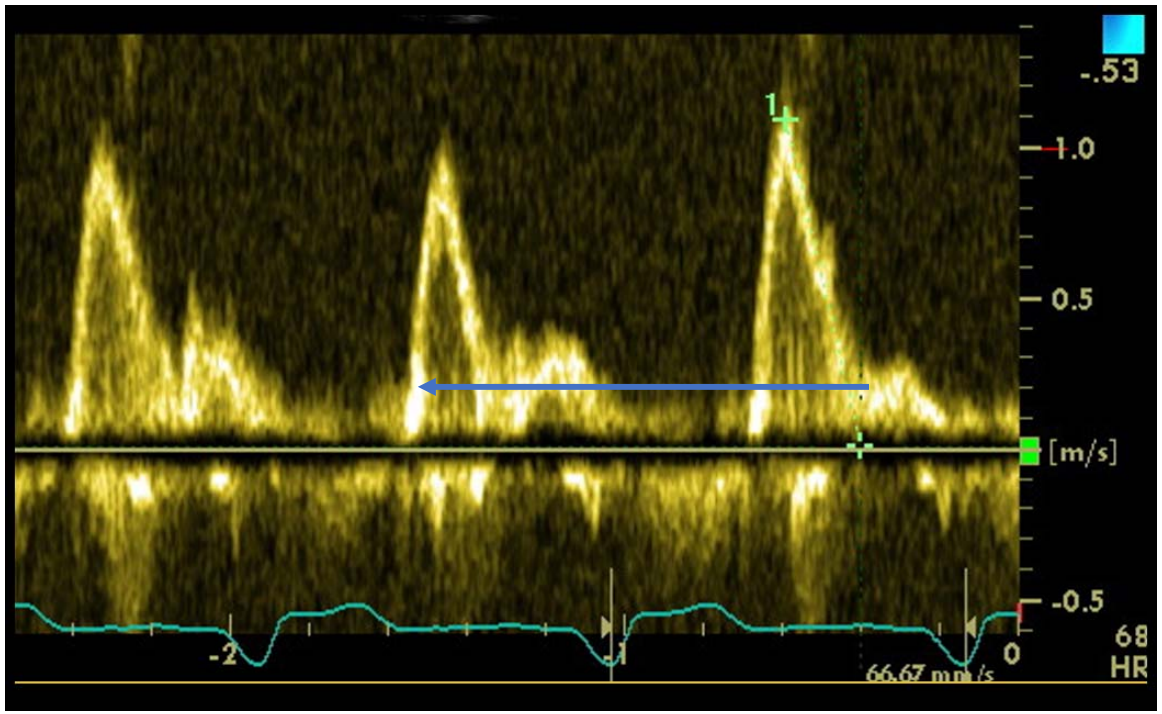


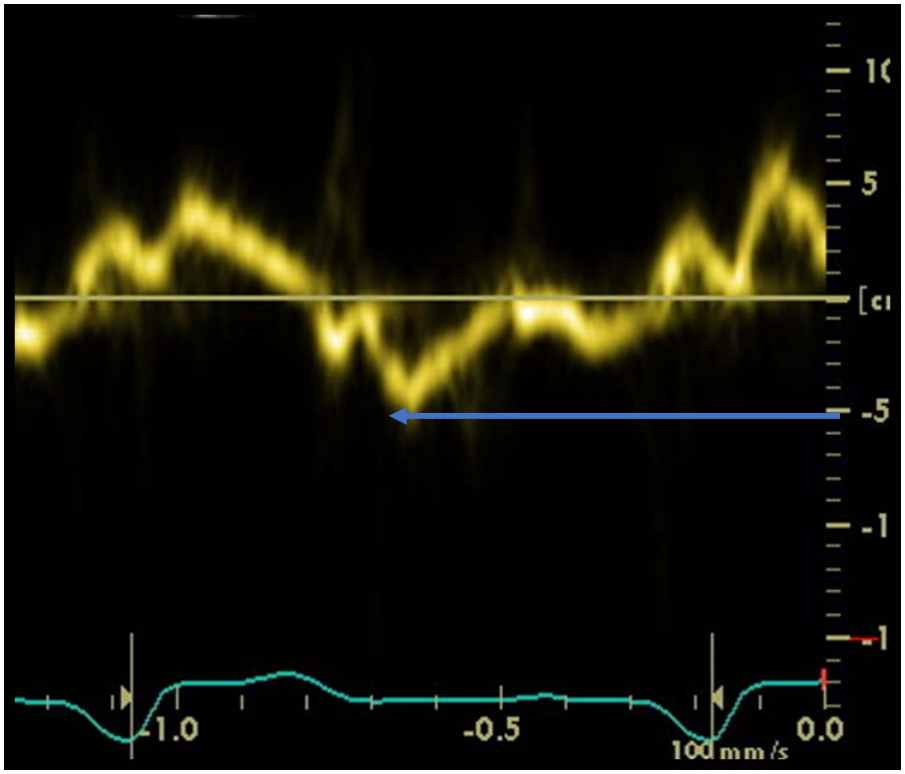
55 yr old white male of Irish descent

- Hypertension
- Unexplained mild neuropathy in feet and hands
- 2007: Complete heart block → Dual chamber pacemaker
- 2008: Recurrent ascites, SOB


American Heart Association.
Freq.: 1.7 MHz/3.4 MHz
FPS: 45.4
V
10
20
68
HR




-.53
1.0
0.5
[m/s]
-0.5
68
HR
1
-2
-1
0
66.67 mm/s


10
5
0
-5
-1
-1
-1.0
-0.5
0.0
100 mm/s

Subsequent Course

- On further history, mother has h/o amyloidosis
- Endomyocardial biopsy: → TTR amyloid
- TTR genetic testing: → T60A (p.Thr80Ala)
- Combined heart and liver transplant 2009

Hereditary Implications

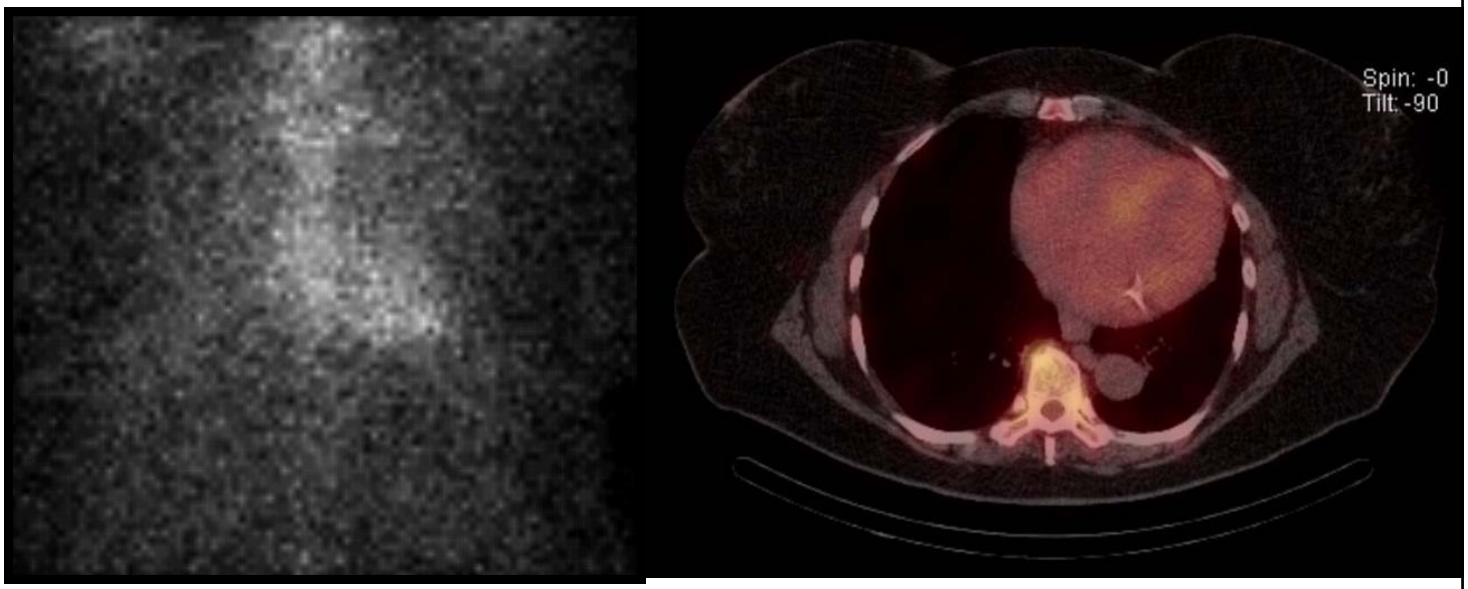
Sister age 60 tested following year (2009)

- T60A mutation

Surveillance for symptoms and for imaging evidence of cardiac amyloid

- CMRI 2016 patchy LGE (age 67)
- TcPYP 2017 grade 3 uptake, H/CL ratio 1.9

Technetium pyrophosphate (TcPYP) scan



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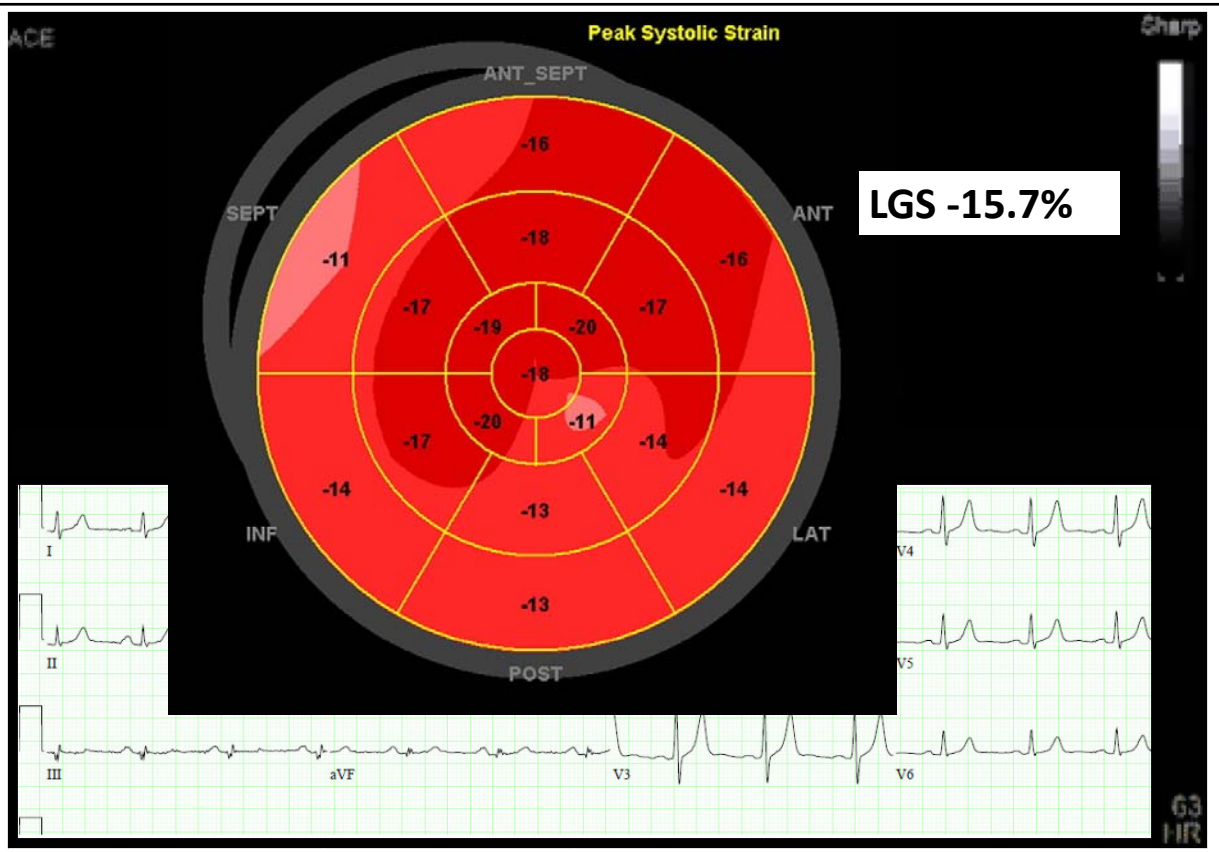
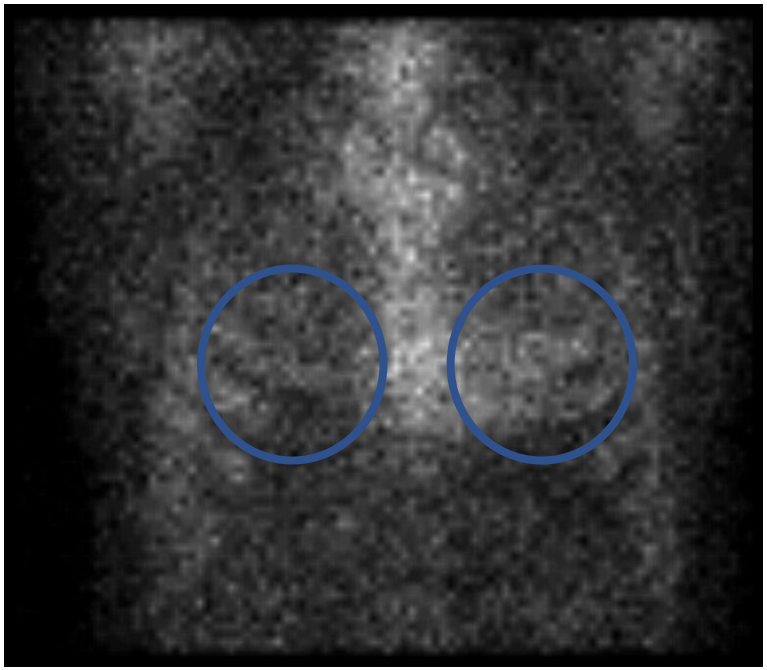
Hereditary Implications

- 41 yr old son tested positive this year
  - **T60A mutation**
- Mild dyspnea on exertion
  - **NT pro BNP 115**
- Bilateral carpal tunnel syndrome

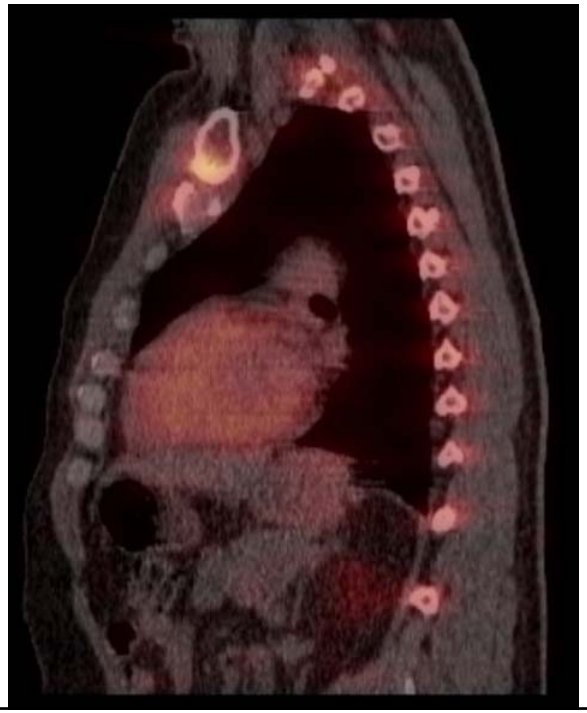

ACE
Peak Systolic Strain
Sharp
ANT_SEPT
SEPT
ANT
INF
LAT
POST
-16
-11
-18
-16
-17
-19
-20
-17
-18
-20
-11
-17
-14
-14
-14
-13
-13
LGS -15.7%
I
II
III
aVF
V3
V4
V5
V6
63
HR

Technetium Pyrophosphate Scan



Grade 2 uptake

Technetium Pyrophosphate Scan



Grade 2 uptake

76-year-old man referred for refractory CIDP

- The patient developed numbness in the feet at age 67.
- At 70, he started having difficulty buttoning his shirt.
- At age 73, his symptoms progressed more rapidly with numbness spreading up to the knees on both sides and mid forearm. His balance became affected, and he started to fall.
- At the age of 76 he started using a stick for balance.

76-year-old man referred for refractory CIDP

- No autonomic or GI symptoms. No dyspnea. He lost about 60 pounds since the onset of his symptoms unintentionally.
- No family history of neuropathy.
- Outside work up showed elevated CSF protein at 91, elevated B6 level at 351, and positive serum GD1a antibody.
- Genetic testing revealed mutation in *TTR* gene c.148G.A (p.Val50Met), a known pathogenic mutation causing hereditary transthyretin amyloidosis.
- A skin biopsy showed amyloid deposition. The patient was started on disease modifying therapy.

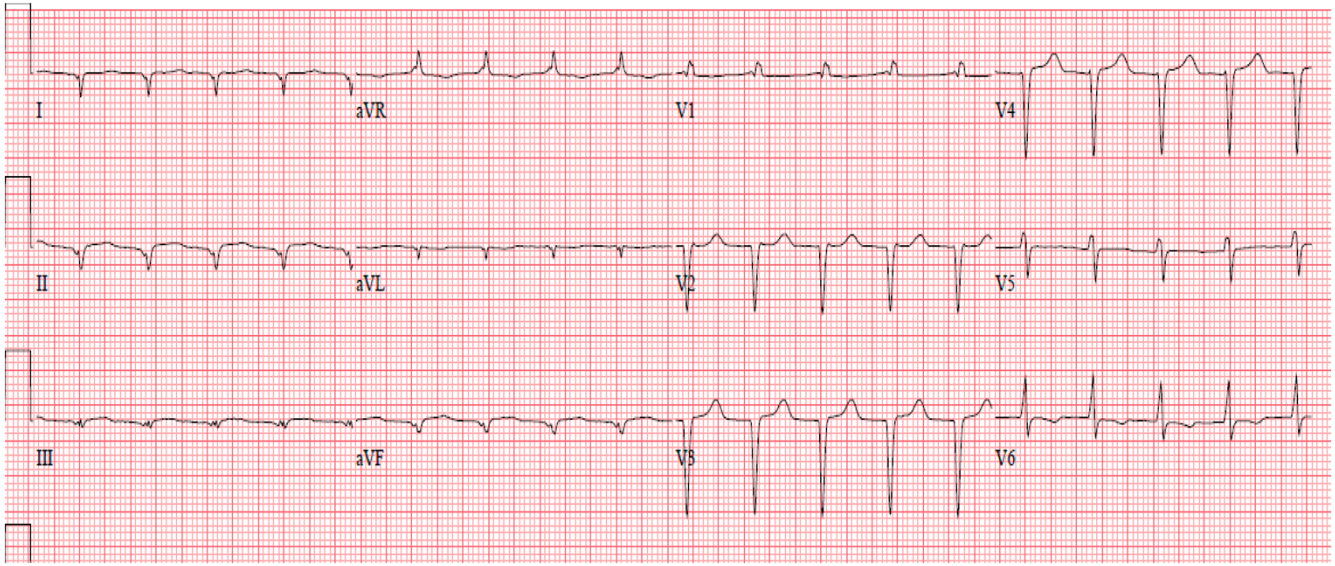
73-year-old African-American Male with Progressive HF Over 5 Years

- **Medical history**
  - Hypertension, CKD, BPH
  - Carpal tunnel release 2012
  - Lumbar spine surgery 2014
- **Presents December 2014 with dyspnea on exertion / ? angina**
  - Cath with distal LAD stenosis (PCI done), 60% diagonal
  - Echo EF 40%, global dysfunction
  - LVEDD 4.2 cm, *"moderate LVH" sept 2.3, PW 2.1 cm*
  - NT pro BNP 1720, Trop T 0.053
  - Diagnosed w/"Ischemic CM" → BB, ACE(-), also on amlodipine for BP

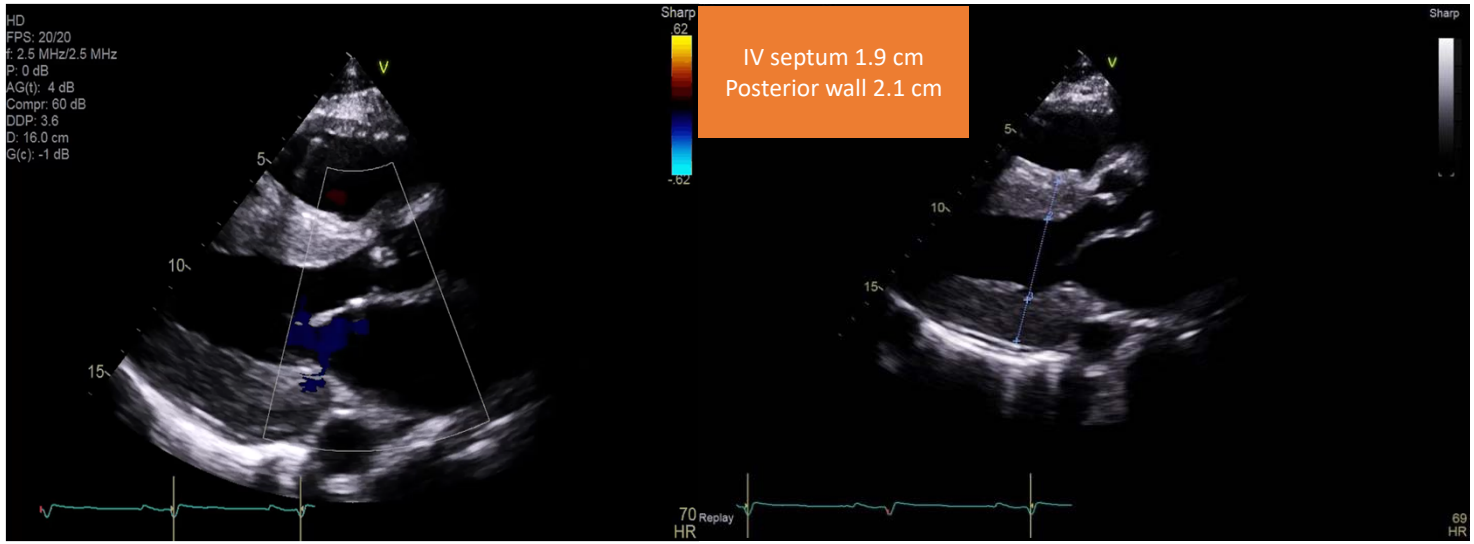
73-year-old African-American Male with Progressive HF Over 5 Years

- Persistently positive Trop T over follow-up period 2014-2019
- Increasing diuretic requirements by 2017-2019, BP decreasing
- 3 hospitalizations for HF, repeat ECHO EF 30%, "severe LVH"
- August 2019 consult CCF:
  - High JVP, low output symptoms
  - ECG low voltage
  - RHC: RA 27 mm Hg, PA 41/27, PCWP 29 (V 32), MVO2 48%, CI 1.2
  - NT pro BNP 8200, Trop T 0.075

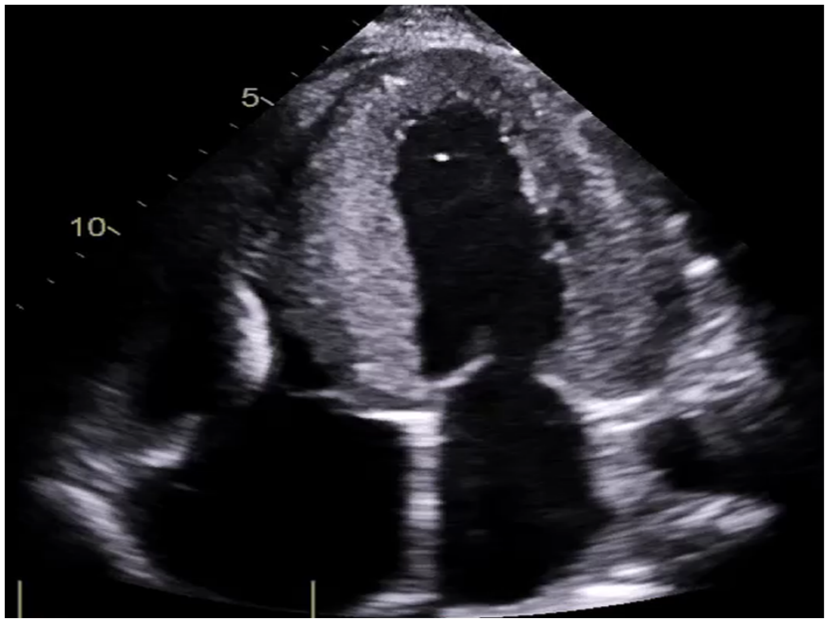
12-Lead Electrocardiogram



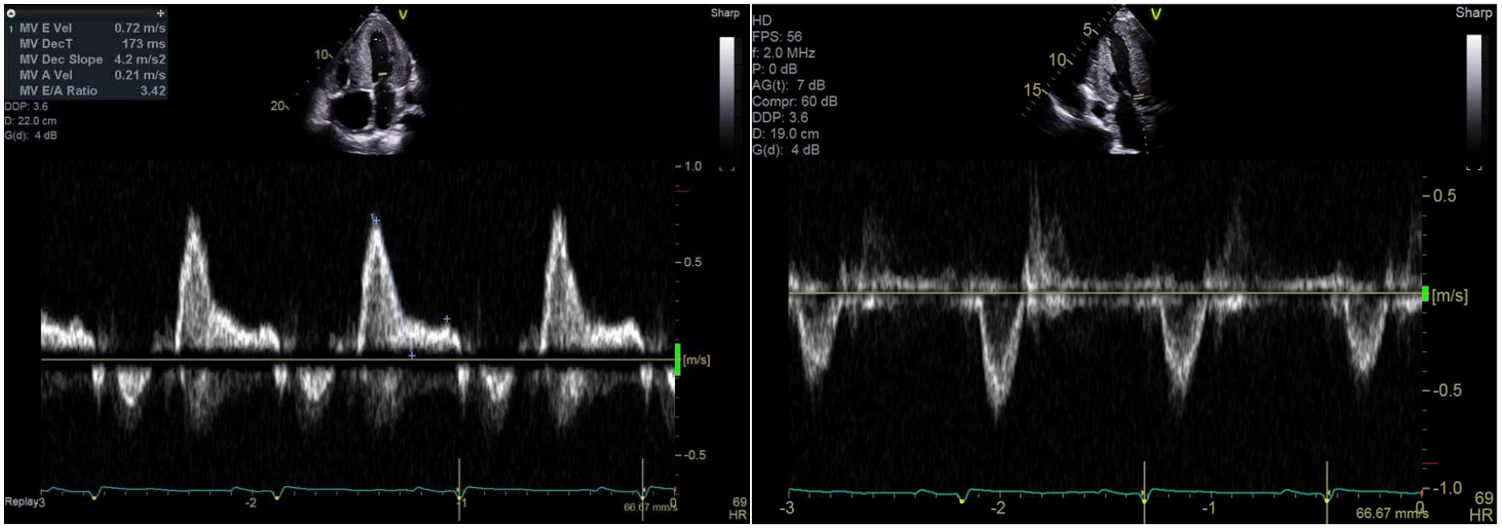
Echo – Parasternal Long Axis View

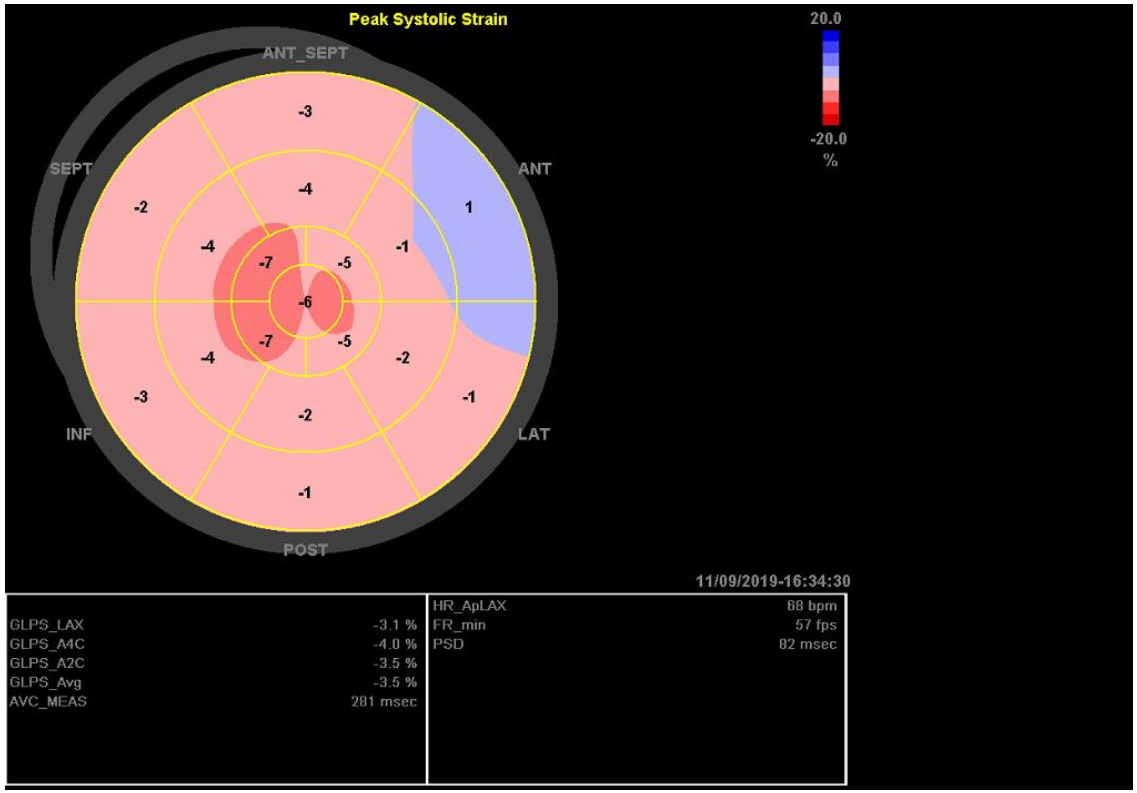


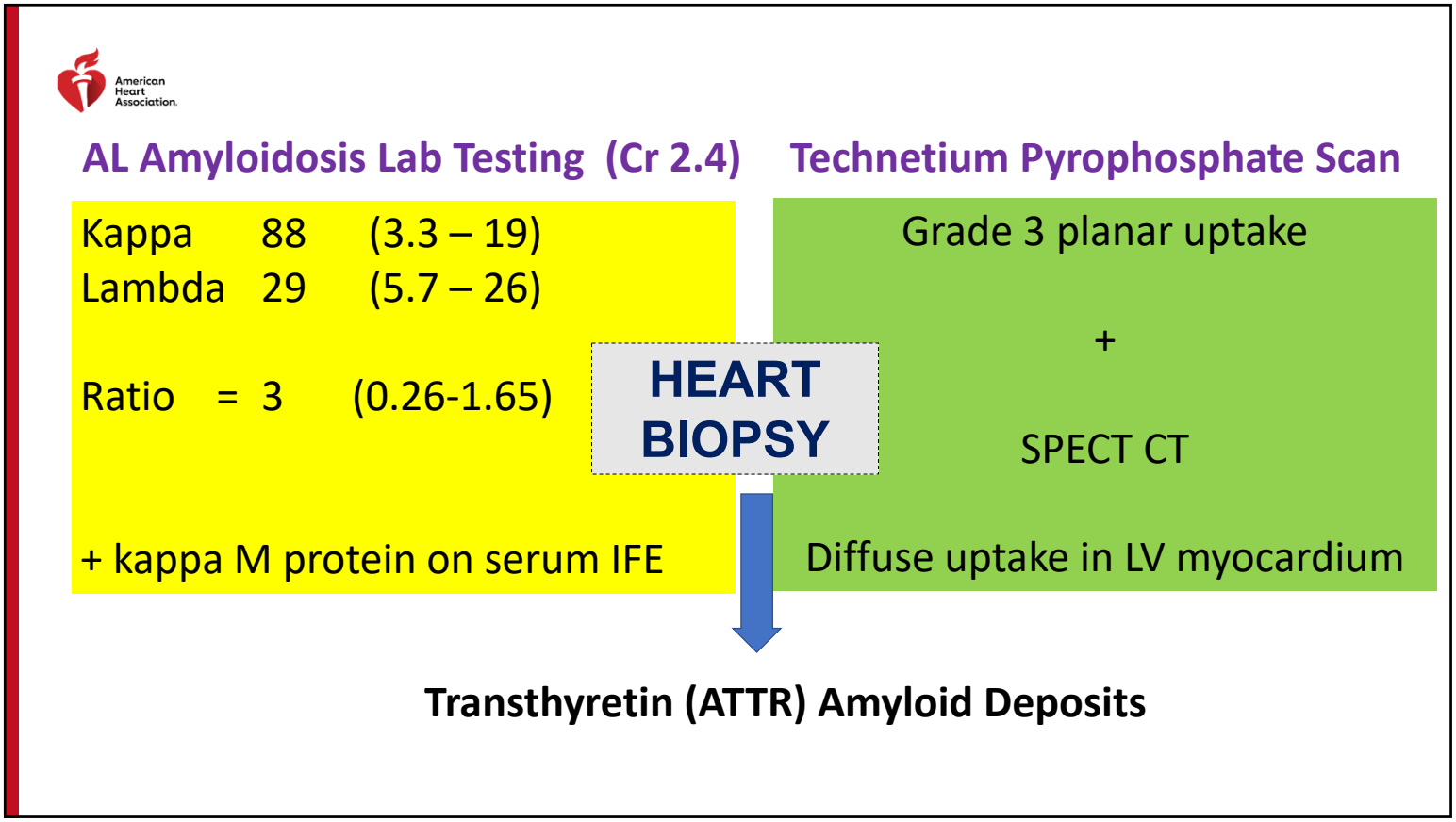
Echo



American Heart Association.




Peak Systolic Strain
20.0
-20.0
%
ANT_SEPT
SEPT
ANT
INF
LAT
POST
-3
-4
-2
1
-4
-1
-7
-5
-6
-7
-5
-4
-2
-3
-1
-2
-1
11/09/2019-16:34:30
GLPS_LAX -3.1 %
GLPS_A4C -4.0 %
GLPS_A2C -3.5 %
GLPS_Avg -3.5 %
AVC_MEAS 281 msec
HR_ApLAX 68 bpm
FR_min 57 fps
PSD 82 msec

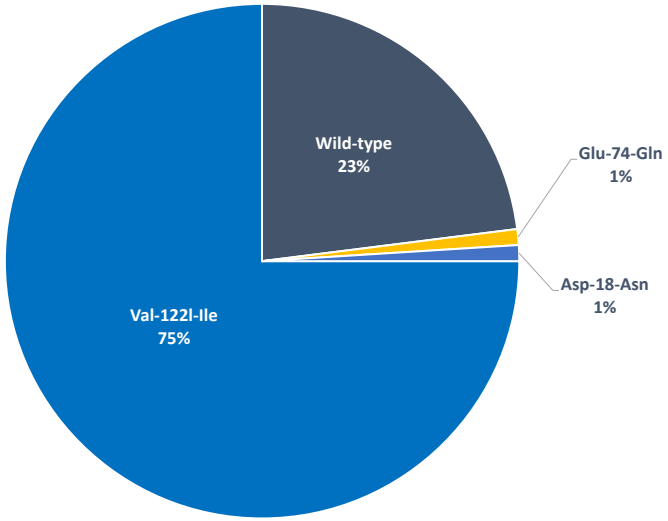

American Heart Association.
AL Amyloidosis Lab Testing (Cr 2.4)
Technetium Pyrophosphate Scan
Kappa 88 (3.3 – 19)
Lambda 29 (5.7 – 26)
Ratio = 3 (0.26-1.65)
+ kappa M protein on serum IFE
HEART BIOPSY
Grade 3 planar uptake
+
SPECT CT
Diffuse uptake in LV myocardium
Transthyretin (ATTR) Amyloid Deposits

73-year-old African-American Male with Progressive HF Over 5 Years

- Summary
  - Carpal tunnel and spinal stenosis around time of presentation
  - Severe LV thickening out of proportion to hypertension
  - Low voltage on ECG
  - African American
- The diagnosis of ATTR amyloidosis was not considered in this patient
- Endomyocardial biopsy showed **ATTR amyloid deposits**
- TTR genetic testing reveals **V122I (p.V142I) variant**

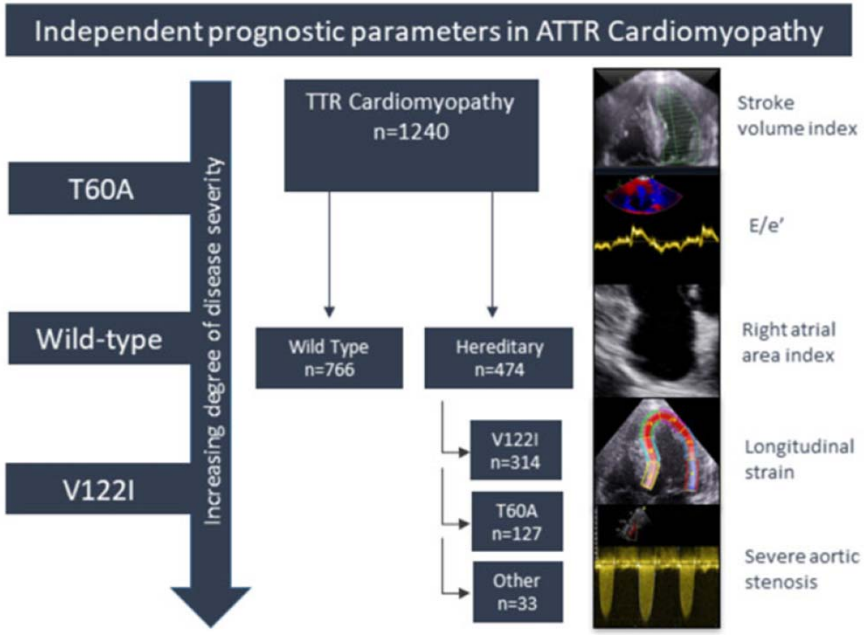
Remember, Not All ATTR-CM Is Secondary to V122I in African Americans

104 African-American patients with ATTR-CM who underwent TTR genetic testing



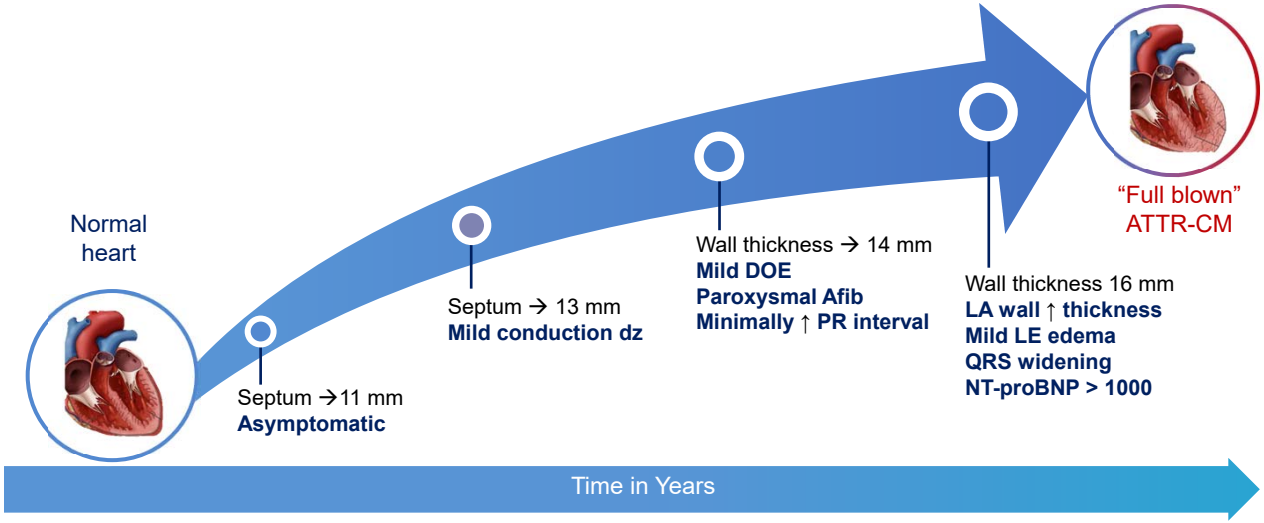
Gabrovsek A, et al. Poster ID#015. Transthyretin Cardiac Amyloidosis in the African American Population. HFSA 2019. Philadelphia, PA.

Echocardiogram in ATTR-CM



Chacko et al., European Heart Journal 2020

Opportunities to Diagnose Along the Disease Continuum



Courtesy of M. Hanna, MD, Cleveland Clinic

Afib, atrial fibrillation; ATTR-CM, transthyretin amyloidosis cardiomyopathy; DOE, dyspnea on exertion; dz, disease; LA, left atrium; LE, left extremity; NT-proBNP, N-terminal pro B-type natriuretic peptide.

Hereditary Transthyretin Amyloidosis Take Home Points

- High index of suspicion
- Carpal tunnel syndrome, spinal stenosis, biceps tendon rupture?
- Unexplained neuropathy, peripheral and/or autonomic?
- Unexplained LVH or heart block, consider this diagnosis?
- Ethnicity & Race Important
  - Irish descent? (p.T80A)
  - African American or Afro-Caribbean? (p.V142I)
  - Portuguese/Japanese/Swedish? (p.V50M)
- Use appropriate diagnostic algorithm
- Make the diagnosis


American
Heart
Association.
Thank You.
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