Special Cardiomyopathies: Focus on Diagnosis

Friday May 13th 3:55 – 4:40 pm

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Dr. Elizabeth Swiggum, Victoria, BC

Dr. François Tournoux, Montreal, QC

Conflict of Interest Disclosures

Dr. Nowell Fine

- **Grants/research support**: Pfizer, Akcea-Ionis, Servier, Takeda, Novartis, Eidos
- **Consulting/speaking fees**: Pfizer, Akcea-Ionis, Sobi, Alnylam, Sanofi-Genzyme, Astra-Zeneca, Takeda

Dr. Elizabeth Swiggum

- **Grants/research support**: Astra Zeneca, BI, Novartis, Pfizer
- **Consulting fees**: BI, BI Lilly Alliance, Novartis, Servier, Bayer
- **Speaker fees**: Astra Zeneca, Bayer, Novartis, Pfizer

Dr. François Tournoux

- **Grants/research support**: Pfizer, Alnylam
- **Consulting fees**: Pfizer, Alnylam, Akcea-Ionis
- **Speaker fees**: Pfizer, Alnylam
- **Other**: Eidos

Objectives

- **Special Cardiomyopathies: Focus on Diagnosis**
- Evaluate diagnostic algorithms for Fabry's, Sarcoid and Amyloid Cardiomyopathies
- Recognize other systemic manifestations of these cardiomyopathies
- Describe the imaging techniques which facilitate diagnosis
- Identify when endomyocardial biopsy is indicated

Cardiomyopathy #1

Nowell Fine MD SM

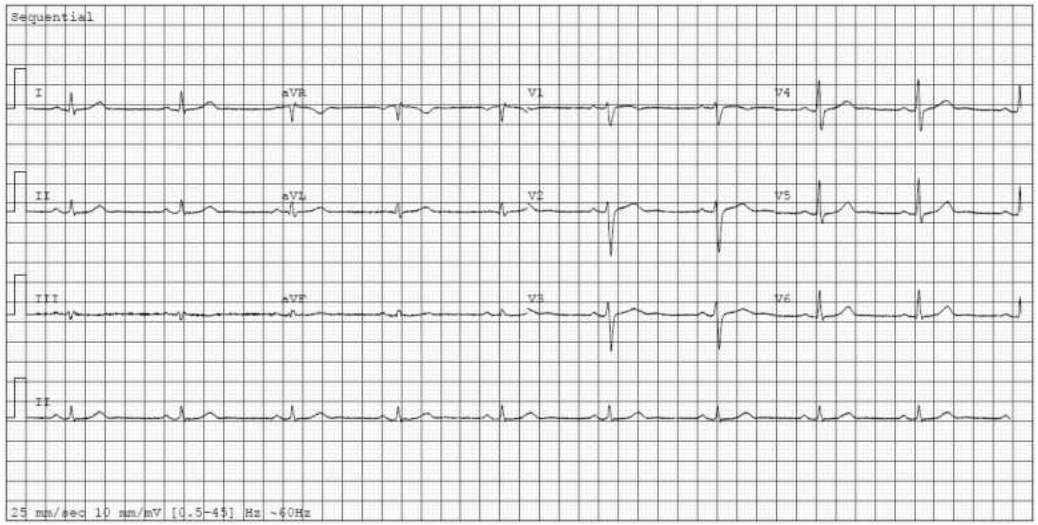
Director of Echocardiography, Heart Failure Cardiologist

Libin Cardiovascular Institute, University of Calgary

Case #1

- 50 yo M
- PMHx – kidney stones
- Fam / social Hx – adopted, Caucasian, no smoking/EtOH/drug use, works from home
- **4 syncopal episodes in 4 weeks**
  - No prodrome, pattern, no associated symptoms, exercising regularly
- Called Fam MD office
  - Rx anxiolytic
  - Advised to hydrate well
- 1 week later, 2 syncopal episodes 3 hours apart at home
- Presents to hospital in **complete heart block**

Case #1



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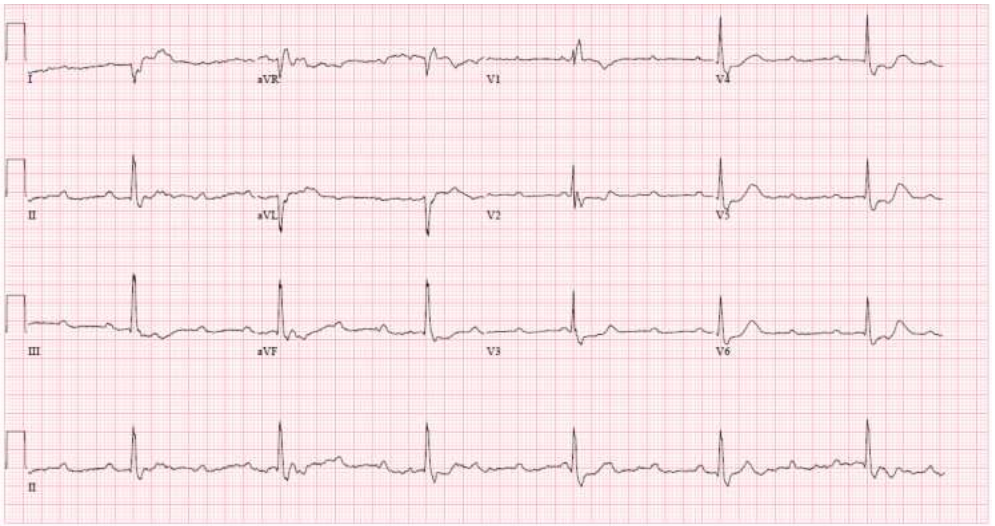
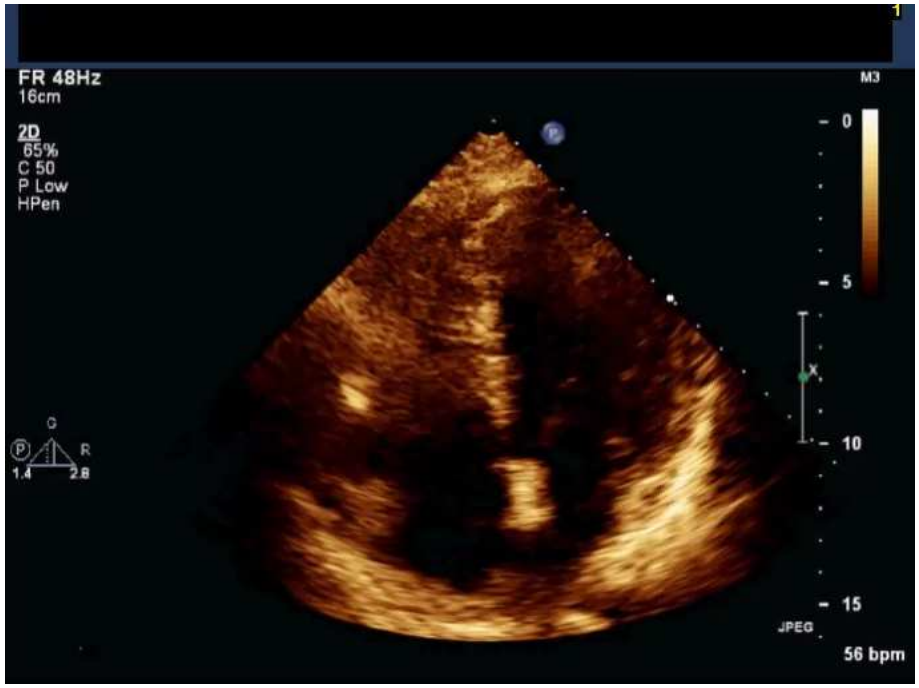


Presentation

Case #1



Echo

- No significant abnormalities

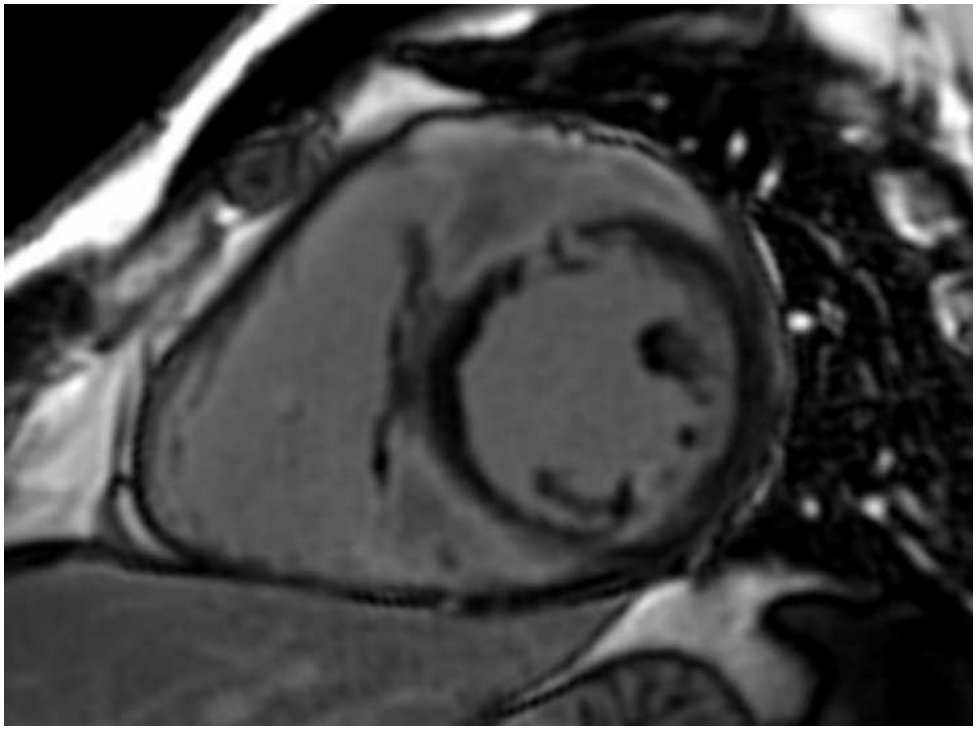
Laboratory

- hs-Troponin-T 80 ng/L
- NTproBNP not done
- Other routine labs normal

Polling Question – Next Investigation?

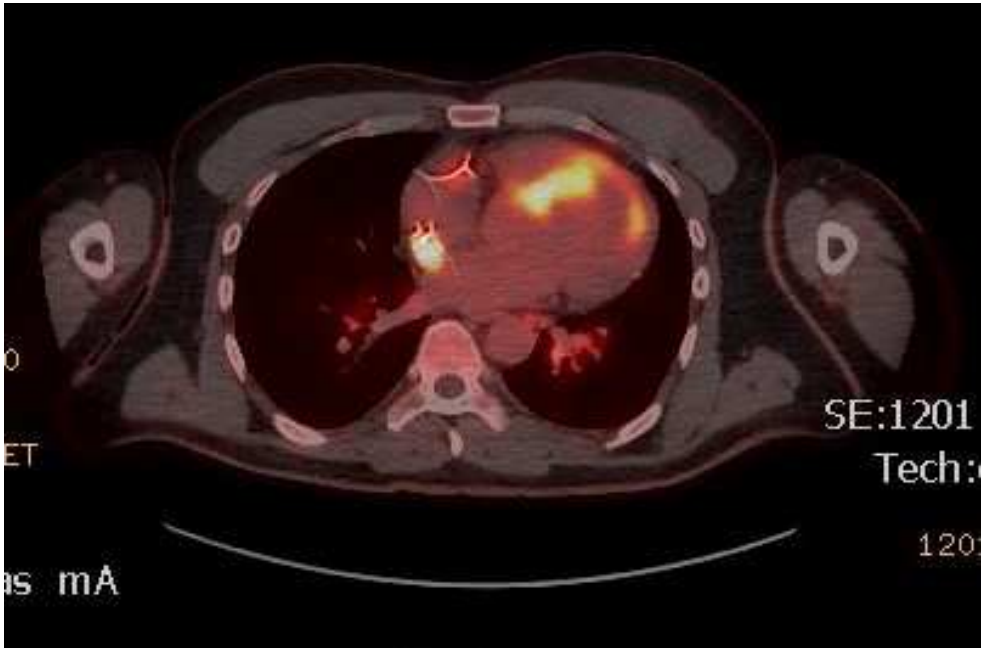
- Electrophysiology study
- Cardiac MRI
- Genetic Testing
- Viral serology
- CT chest
- Cardiac biopsy
- Something else

Case #1



CMR

- Extensive basal LGE

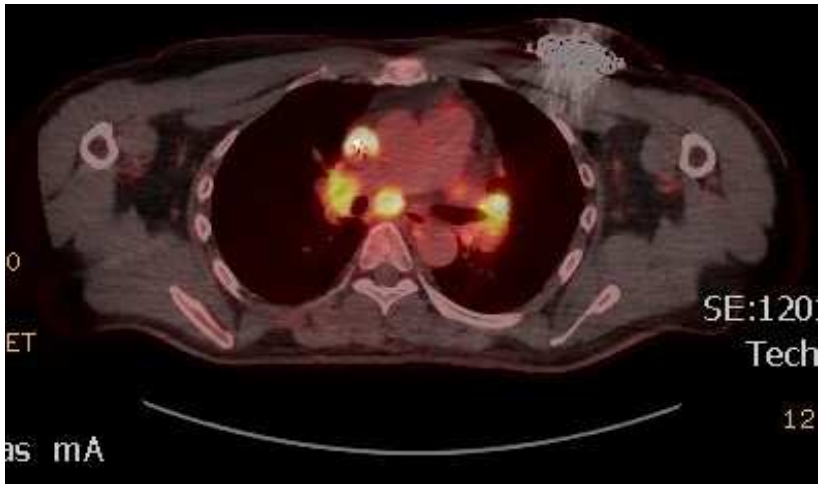


FDG-PET

- Extensive uptake

Case #1

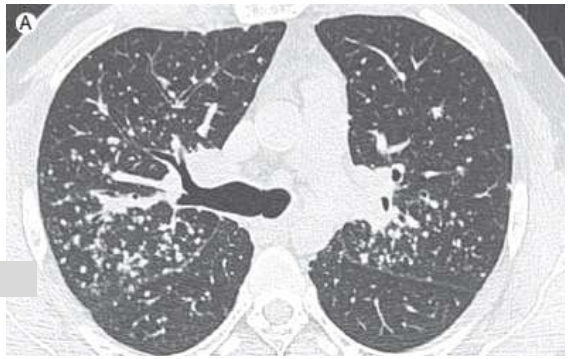
- Diagnosis
  - **Cardiac sarcoidosis**
  - Extensive thoracic and abdominal lymphadenopathy and splenic involvement
- Endobronchial LN biopsy
  - Confirm non-caseating granulomas
- ICD-PPM
- Immunosuppression



FDG-PET

- Thoracic lymphadenopathy

Sarcoidosis



- Granulomatous disease, often multisystem
- Prevalence ≈ 50/100,000
- Highest in northern European and African
- Age ≈ 25-60 years
- **>90%** pulmonary involvement

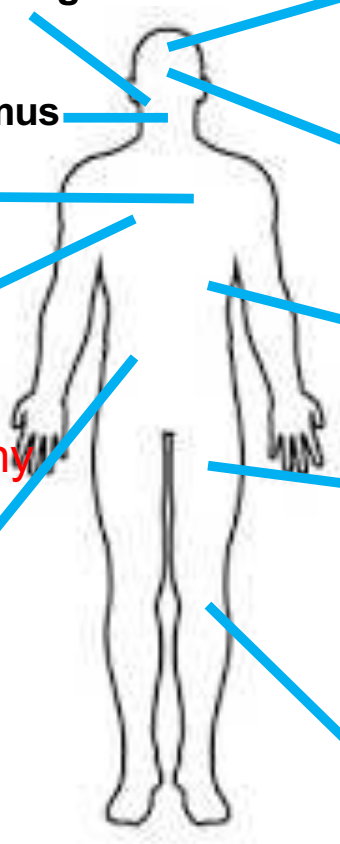
Exocrine Gland Swelling
- Salivary, Parotid

Thyroid, Hypothalamus

Heart

Pulmonary
- Bilateral hilar lymphadenopathy
- Reticular opacities

Renal
- Nephrocalcinosis, nephrolithiasis



Neurologic
- Encephalopathy
- Meningitis

Ocular
- Uveitis-pain and redness
- Lacrimal glands

Lymph, Liver, Spleen
- Lymphadenopathy
- Hepato-splenomegaly

Skin
- Erythema nodosum-painful nodules mostly on lower extremities
- Papular lesions on head and neck
- Plaque-like lesions on torso

Musculoskeletal
- Polyarthritis/arthralgia

Valeyre. Lancet 2014;383:1155

Cardiac Sarcoidosis

- **5%** have cardiac involvement
- Often **minimal extracardiac manifestations**
  - 2/3 isolated cardiac involvement
  - 20% may have clinically silent cardiac involvement
- Highly suggestive manifestations include new / unexplained
  - AVB - Mobitz II or 3rd degree AVB in patient <60 years
  - Sustained monomorphic VT
    - SVT less common
  - Syncope or sudden cardiac arrest
  - Cardiomyopathy / heart failure
  - Biopsy proven extracardiac sarcoidosis with symptoms/ECG/echo findings suggesting cardiac involvement
    - CMR/PET otherwise not necessary to screen
- **DDx**
  - Broad
  - Other myocarditis / inflammatory cardiomyopathy – lymphocytic, giant cell, ARVC, genetic CMP

Birnie. Eur Hrt J 2017;38:2663

Diagnostic Approach

- **ECG**
  - Nonspecific
  - AVB
  - Conduction disease
  - Tachyarrhythmia
- **Echo**
  - Nonspecific findings
  - Septal thinning (especially basal)
  - LV or RV wall thickening possible (acute inflammation)
  - RWMA non-coronary distribution, aneurysms
  - PH assessment for pulmonary sarcoidosis
- **Biomarkers**
  - Nonspecific
  - Serum ACE and lysozyme have limited utility
  - Troponin and NTpro/BNP may be elevated – especially if active disease or heart failure

Birnie. Eur Hrt J 2017;38:2663

Diagnostic Approach

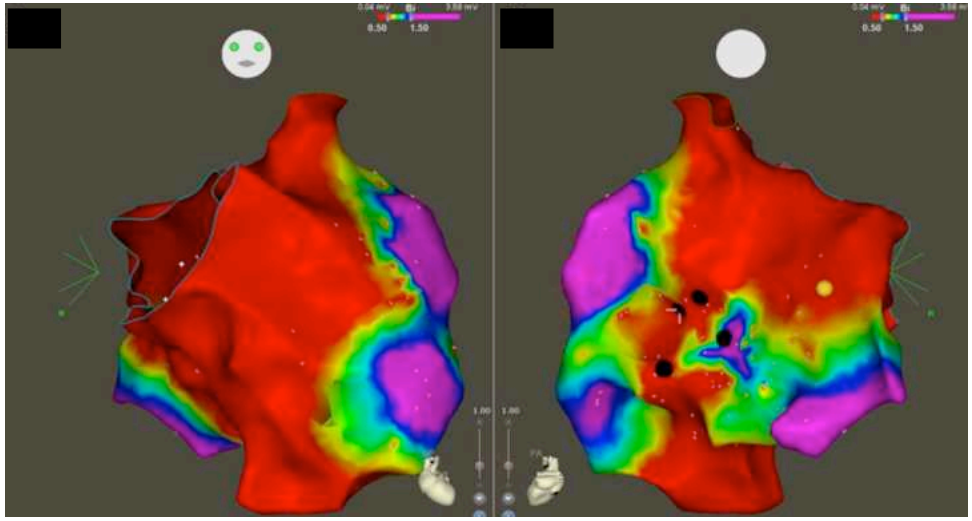
- **CMR**
  - LGE-multifocal, patchy, subepicardial, often basal septum and lateral walls
    - Other patterns possible
  - **Diagnostic**

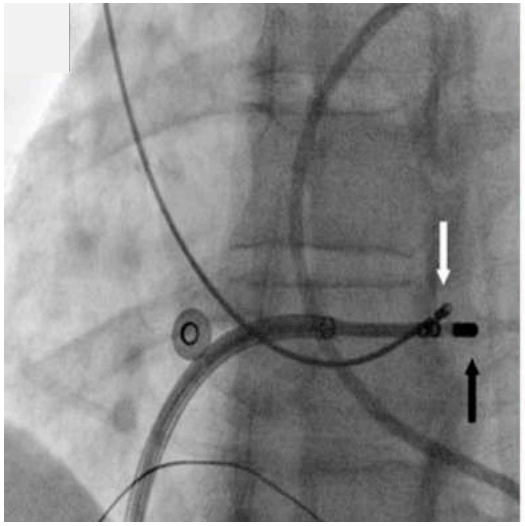
- **FDG-PET**
  - Focal or diffuse cardiac uptake
  - Marker of disease activity
  - Suppression of physiologic FDG cardiac uptake
    - Pre-procedure fasting (≥12 hours), low-carb fat-rich meals day before
  - Recommended if CMR negative or inconclusive with clinical findings suggestive, or to **guide immunosuppression therapy**
  - Limited whole body images
    - Extracardiac Bx sites, LN

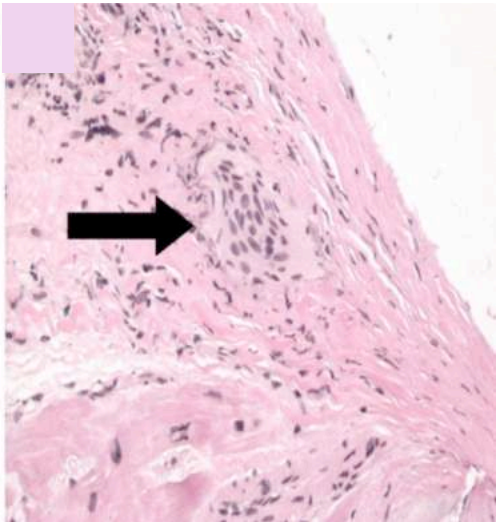
Birnie. Eur Hrt J 2017;38:2663

Role for Biopsy

- Lung / lymph node biopsy first if involvement seen by imaging → high yield
- If extracardiac biopsy unavailable, **cardiac biopsy** may be necessary to confirm Dx
  - Risk of sampling error due, low sensitivity ≈ 20-30%
  - **Guided** by electro-anatomic mapping or CMR / PET







Birnie. Eur Hrt J 2017;38:2663

Diagnostic Criteria – Expert Consensus

- (1) **Histological diagnosis from myocardial tissue**
  - Presence of non-caseating granuloma on histological examination of myocardial tissue (no alternative cause)
- (2) **Clinical diagnosis** from non/invasive, CS is probable if:
  - (a) There is a **histological diagnosis of extra-cardiac sarcoidosis**, **AND**
  - (b) ≥1 of
    - Steroid/immunosuppressant responsive cardiomyopathy or heart block
    - Unexplained LVEF <40%
    - Unexplained sustained VT
    - Mobitz type II 2º HB or 3º HB
    - Patchy uptake on cardiac FDG-PET
    - Late gadolinium enhancement on CMR
    - Positive gallium uptake, **AND**
  - (c) Other causes excluded

Birnie. Eur Hrt J 2017;38:2663

Cardiomyopathy #2

Elizabeth Swiggum MD, FRCPC, FCCS

Medical Director HFC Royal Jubilee Hospital, Victoria B.C.

Clinical Associate Professor UBC

Medical Chair Heart Failure and Chronic CVD Cardiac Services BC

MMP – you get what you get….

- 72 y.o female

Initially reviewed in 2018 for atypical chest pain at age 68 yr

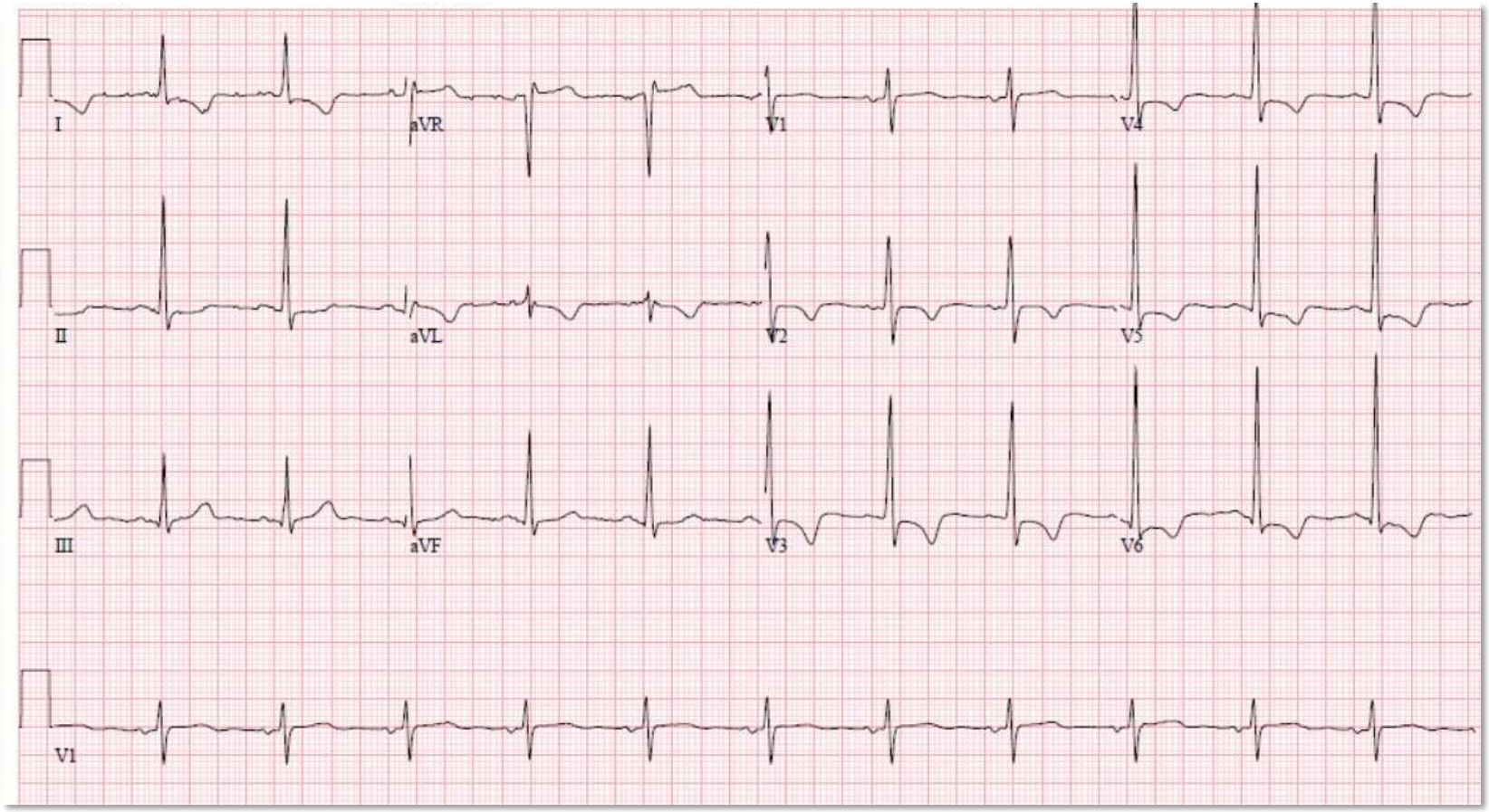
  - 5-6 yr occasional chest pain
  - Dyslipidemia
  - HTN
  - ex-smoker
  - Inactive

- Hearing aids – bilateral
- Bilateral leg pain with walking
- Father died age 68 - SCD

- **Medications:**
  - Telmisartan 80 mg daily
  - Other non-cardiac meds
- Physical Exam:
  - 139/71, HR 78 BPM
  - Normal Heart sounds
  - JVP 2 cm ASA
  - No edema, no rash

- Labs –eGFR 64, Urine protein +
- LDL 3.44 – not on statin

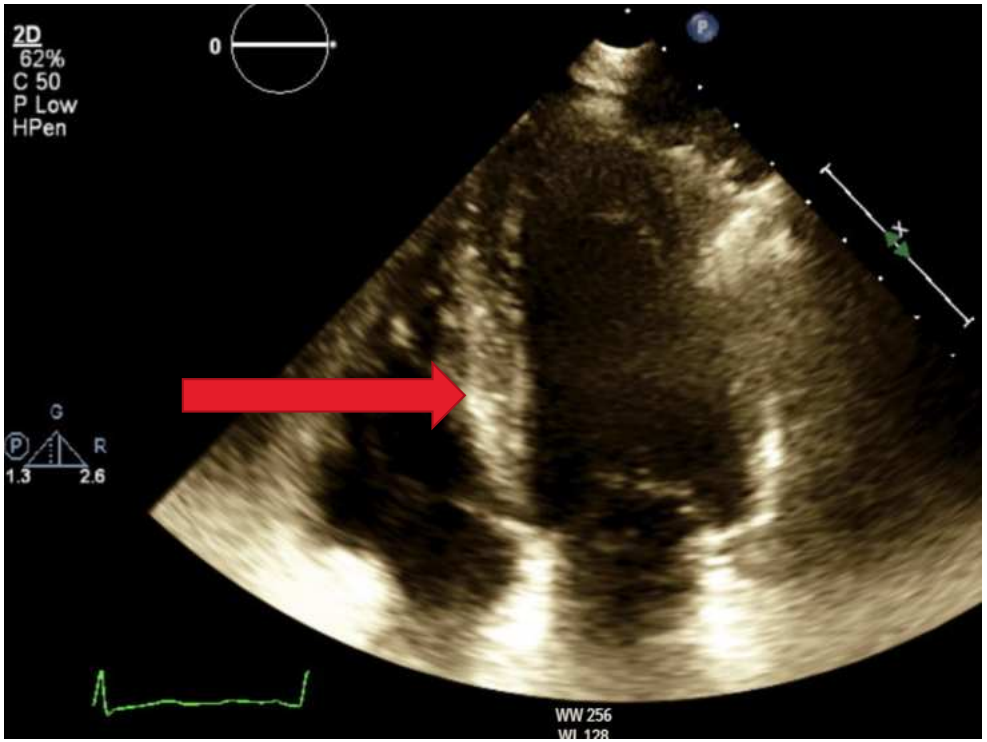
ECG 2020- MMP



Testing was arranged…

Diagnositc testing – LV is a bit thick

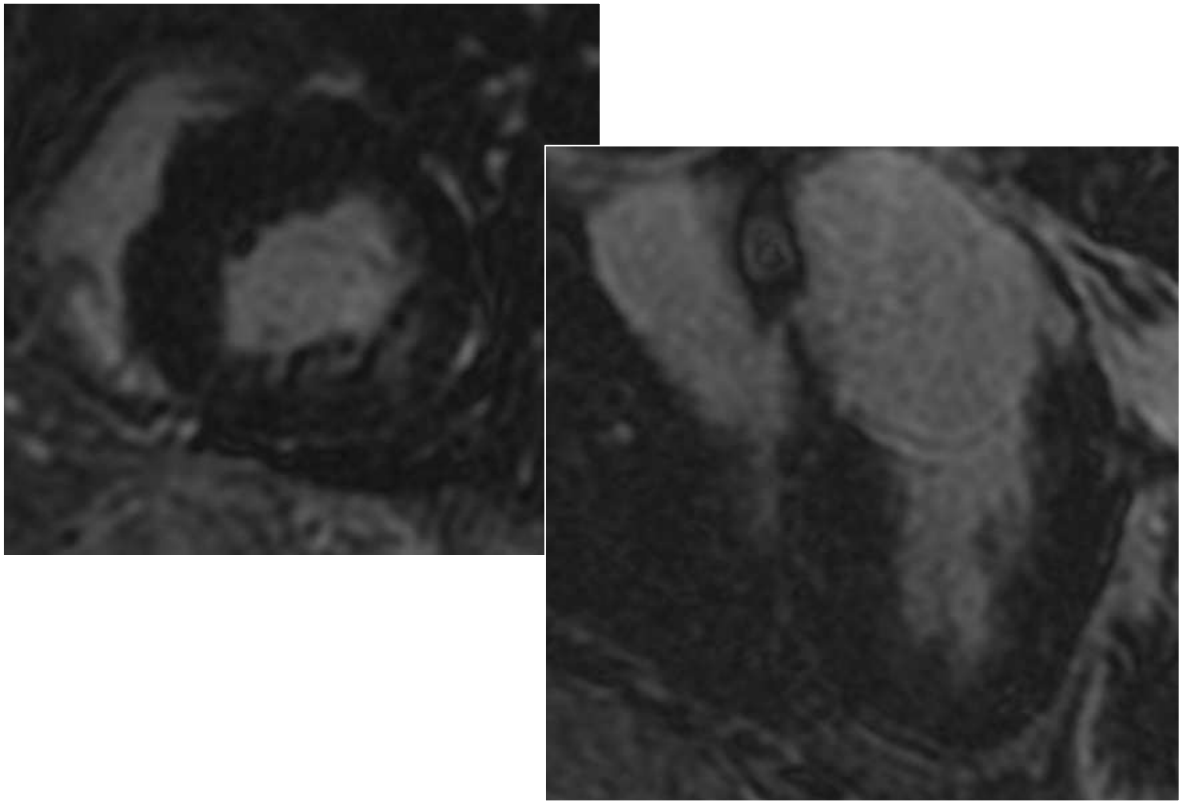
- Echo March 2019 (2022 poor quality)
  - LVEF 60-65%
    - AV, MV sclerosis, no stenosis
  - LVIDd 4.3 cm, 13/13 mm thickness, LAVi 37.1 mL/m2



cMRI Sept 2019

- T1 mapping not performed

- LVEF 62%
- Anteroseptal thickness 15 mm
  - No obvious scar on delayed gadolinium enhancement



Audience Poll

Left Ventricular Hypertrophy should lead to:

1. Better BP control – patient has hypertension
2. Medical Genetics referral to investigate cause such as hypertrophic cardiomyopathy
3. Endomyocardial biopsy
4. Repeat testing – suveillance

Medical Genetics Referral to explore possible HCM

Family History

- 2 healthy adult children
- 1 sister (healthy) – age 73
- 1 brother – age 78 (heart rhythm problem)
- Father died age 68 – cardiac arrest
  - Paternal grandfather died in 50's – unknown cause
- Mother died at 92 stroke

- HCM and CMO panel done

Not expecting those results

- GLA gene mutation (c.775C>T, p.Pro259Ser)
- Glycosphingolipid level (LYSO-GB3)
  - 6.4 ng/mL (ref <1.8 ng/mL)

- Proteinuria mild
- Normal sweating
- No neuropathy

Fabry Disease

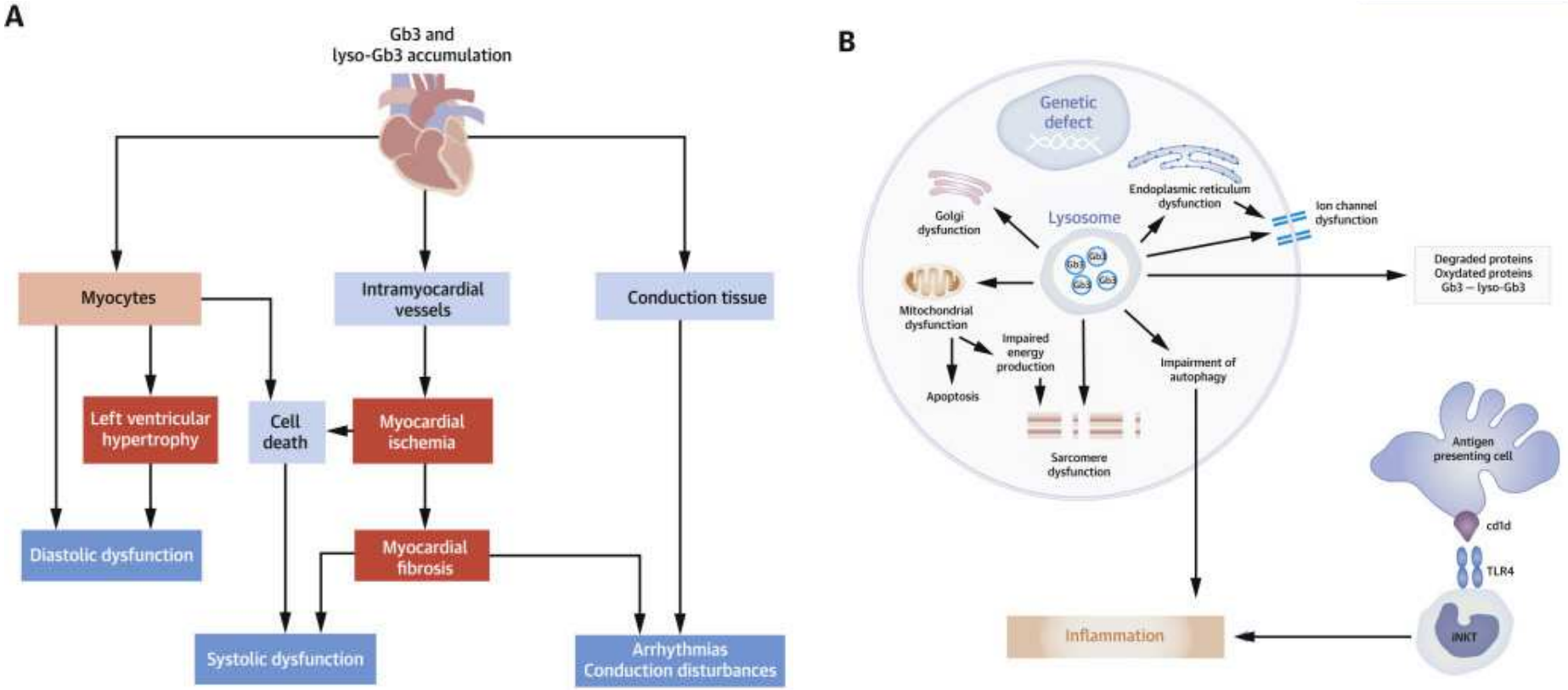
- X-linked autosomal recessive disease
  - pan ethnic, pathogenic variants in the GLA gene

  - Lysosomal enzyme depletion – α-galactosidase A
  - Breaks down glycophospholipids
  - Leads to accumulation of lysosomal globotriaosylceramide (Gb3) and related globotriaosylsphingosine (lyso-Gb3)
    - Heart
    - Skin
    - Kidneys
    - Vasculature
    - Peripheral Nervous system

Flags by decade

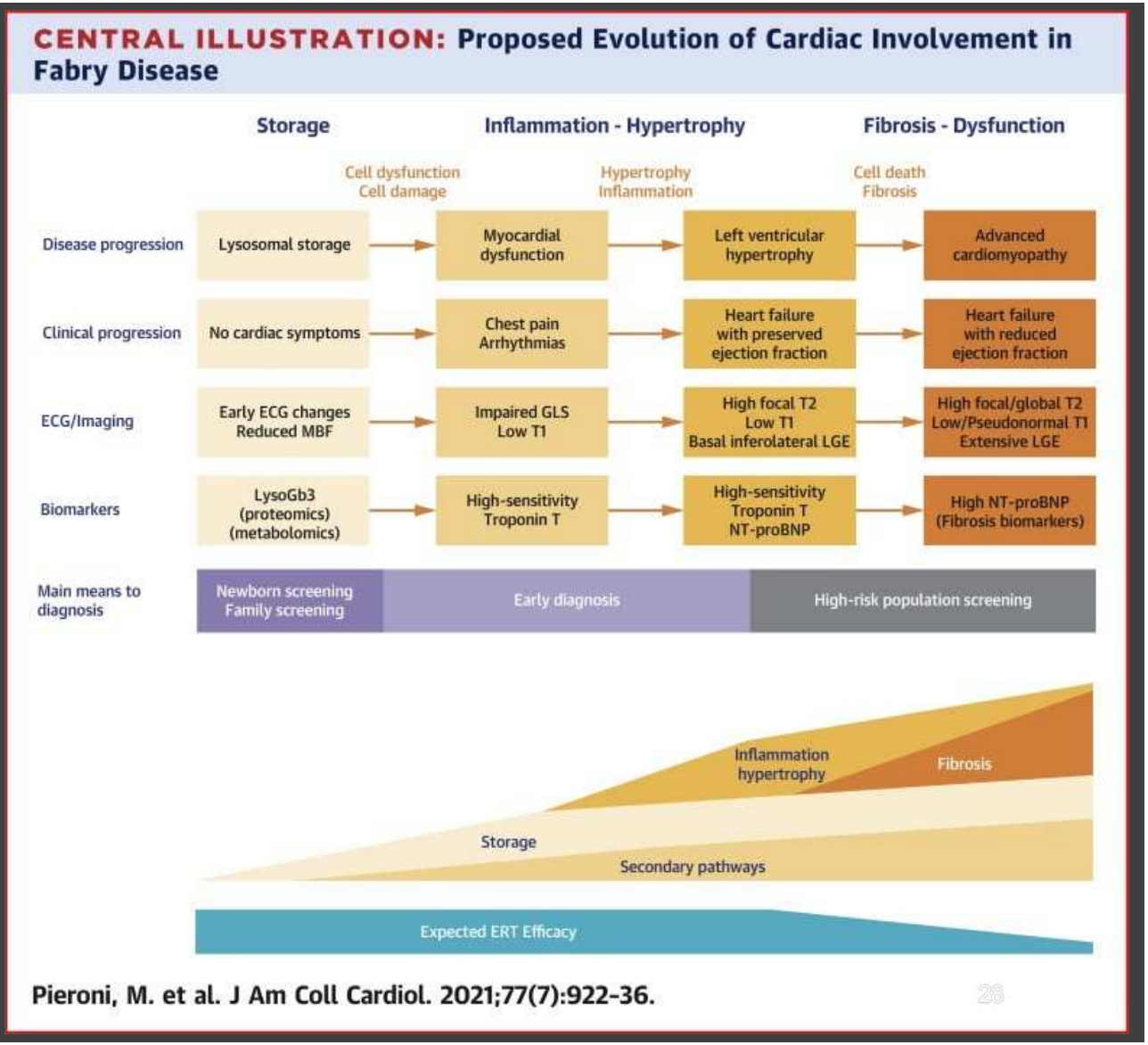
Extra-Cardiac Red Flags			Cardiac Red Flags		
Presenting Decades of Age	Any time	Family history of renal failure and/or stroke	Family history of LVH, particularly if no evidence of male-to-male transmission	History	Diagnostic Tool
	1–2	Neuropathic pain			
	1–2	Gastrointestinal symptoms	Short PQ interval†	Electrocardiography	
	1–2	Angiokeratomas	Bradycardia		
	1–2	Cornea verticillata*	Chronotropic incompetence		
	1–2	Hypohidrosis, heat/cold, and exercise intolerance	Atrioventricular blocks†		
	1–2	Albuminuria	LVH with normal systolic function	2D-echocardiography	
	3–4	Juvenile and/or cryptogenic TIA/stroke	Reduced global longitudinal strain		
	3–4	Hearing loss (either progressive or sudden)	Mild-to-moderate aortic root dilation		
	3–4	Dolichoectrasia of the basilar artery, chronic white matter hyperintensities at brain MRI	Mitral and aortic valve thickening with mild-to-moderate regurgitation		
	3–4	Proteinuria	Hypertrophy of papillary muscles	Cardiac Magnetic Resonance	
	3–4	Renal failure	Mid-layer posterolateral late gadolinium enhancement		
	3–4	Lymphedema	Low native T1		

Pathophysiology of Fabry



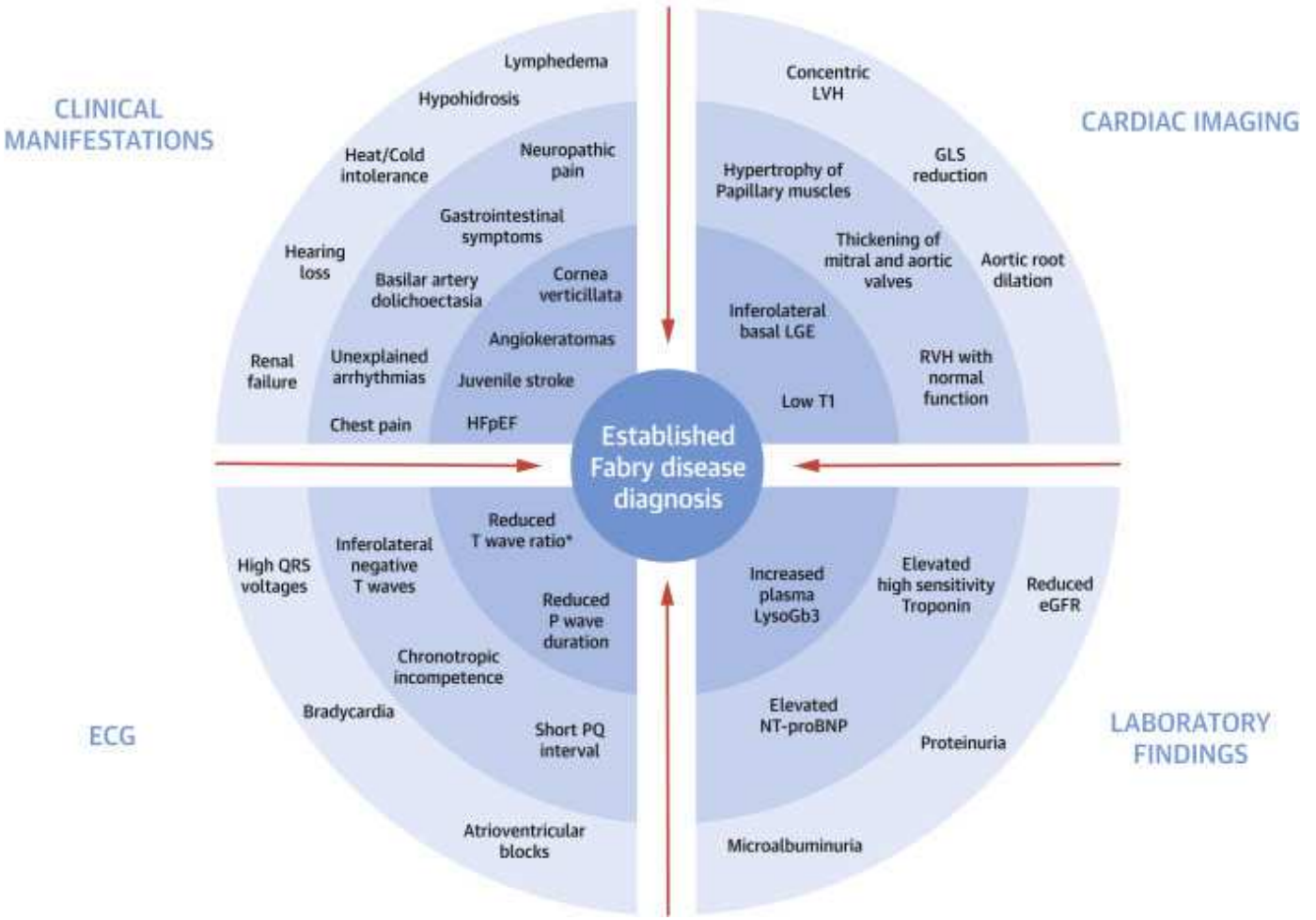
Pieroni JACC 2021; 77:922 -36

Diagnosis and Staging



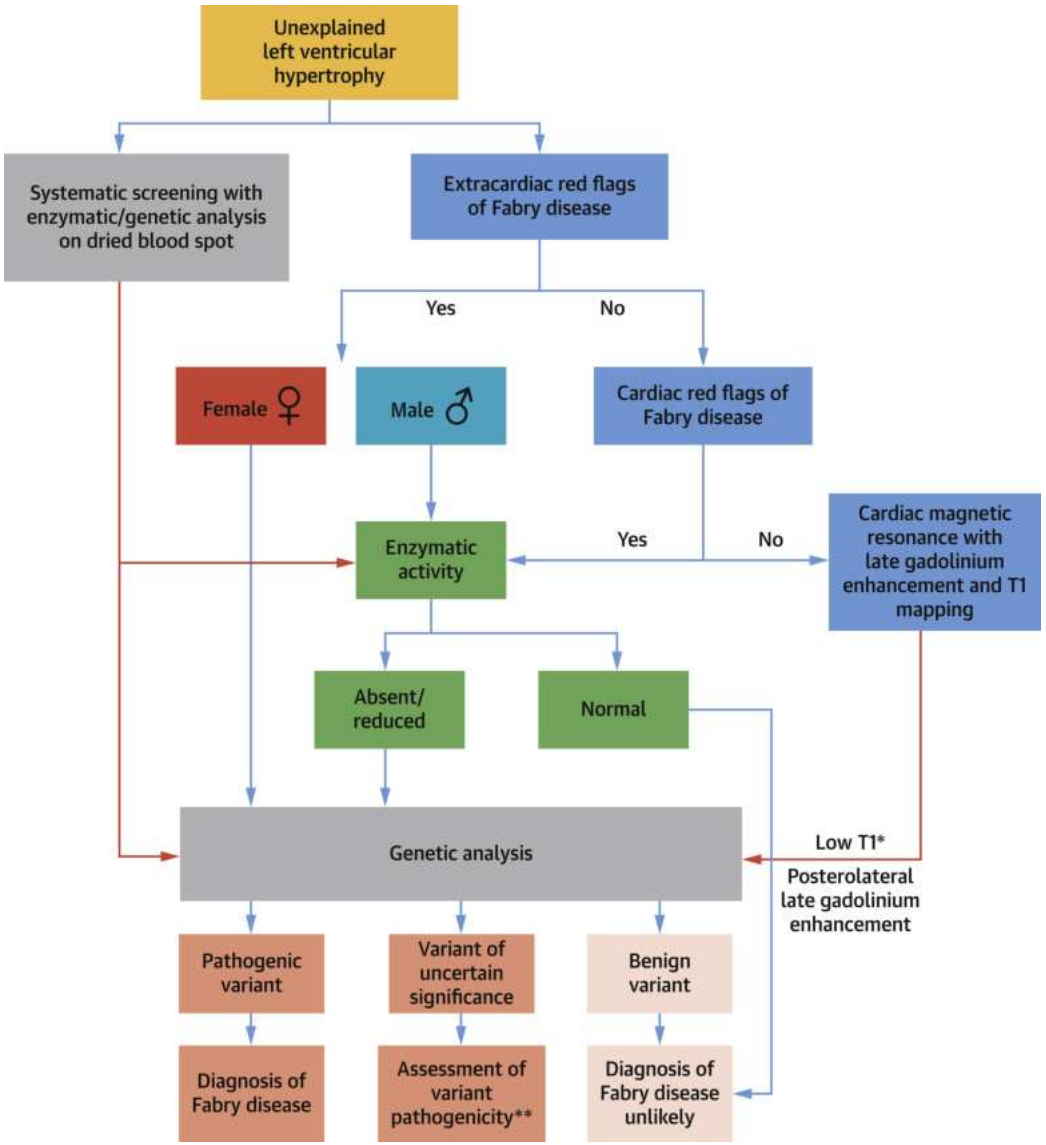
Pieroni, M. et al. J Am Coll Cardiol. 2021;77(7):922-36.

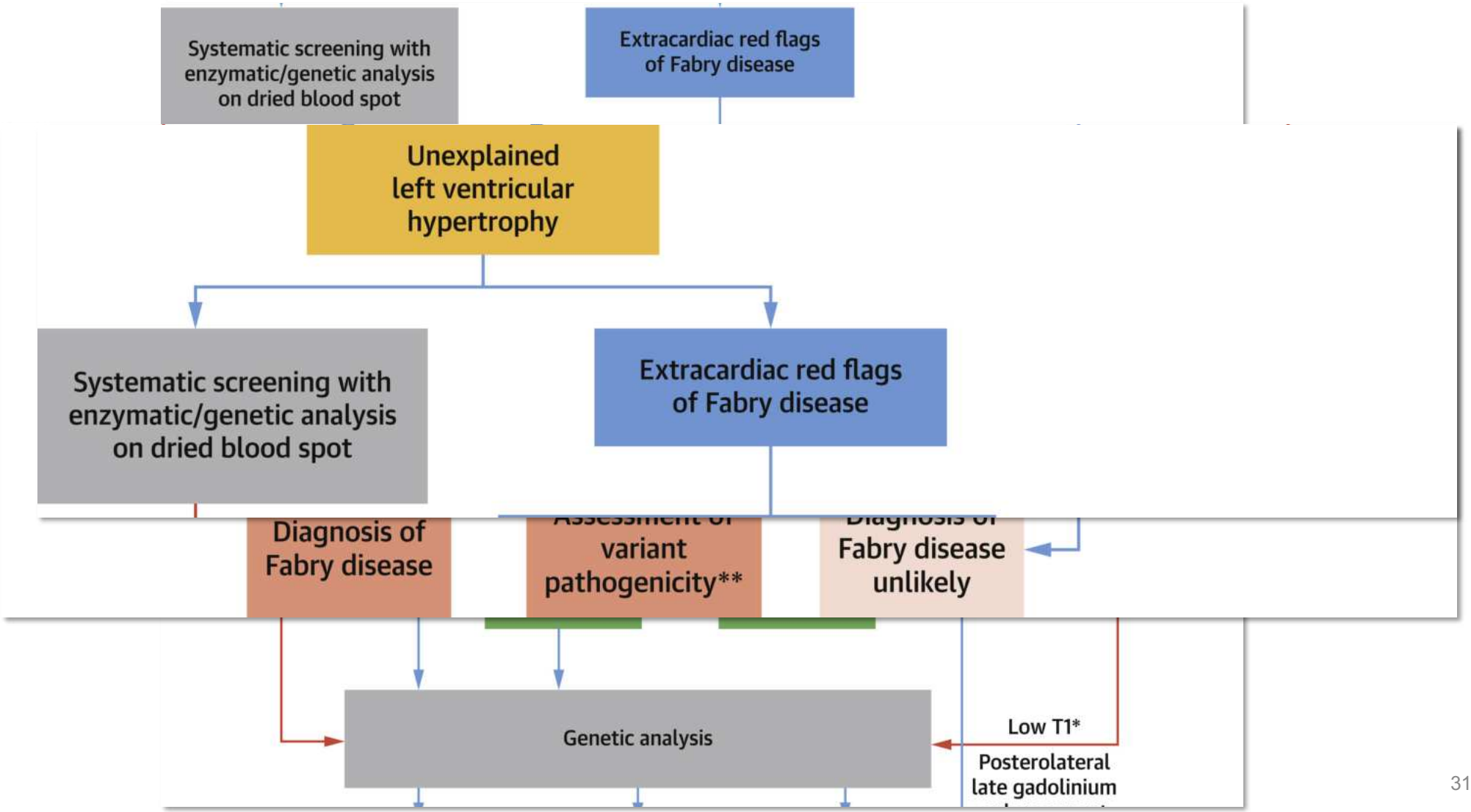
Red Flags

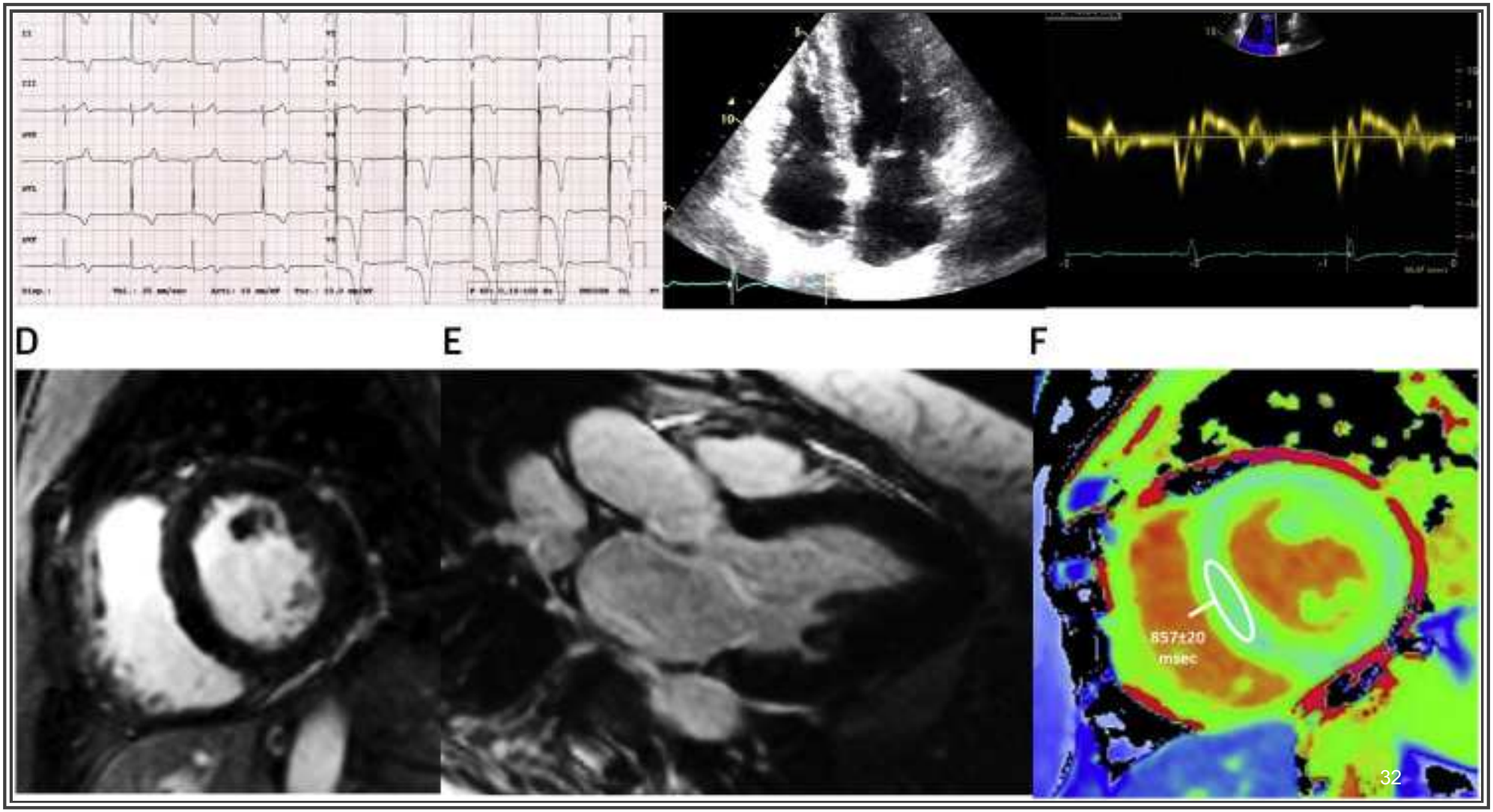


Pieroni JACC 2021; 77:922 -36

Idiopathic LVH




Systematic screening with enzymatic/genetic analysis on dried blood spot
Extracardiac red flags of Fabry disease
Unexplained left ventricular hypertrophy
Systematic screening with enzymatic/genetic analysis on dried blood spot
Extracardiac red flags of Fabry disease
Diagnosis of Fabry disease
variant pathogenicity**
Fabry disease unlikely
Genetic analysis
Low T1*
Posterolateral late gadolinium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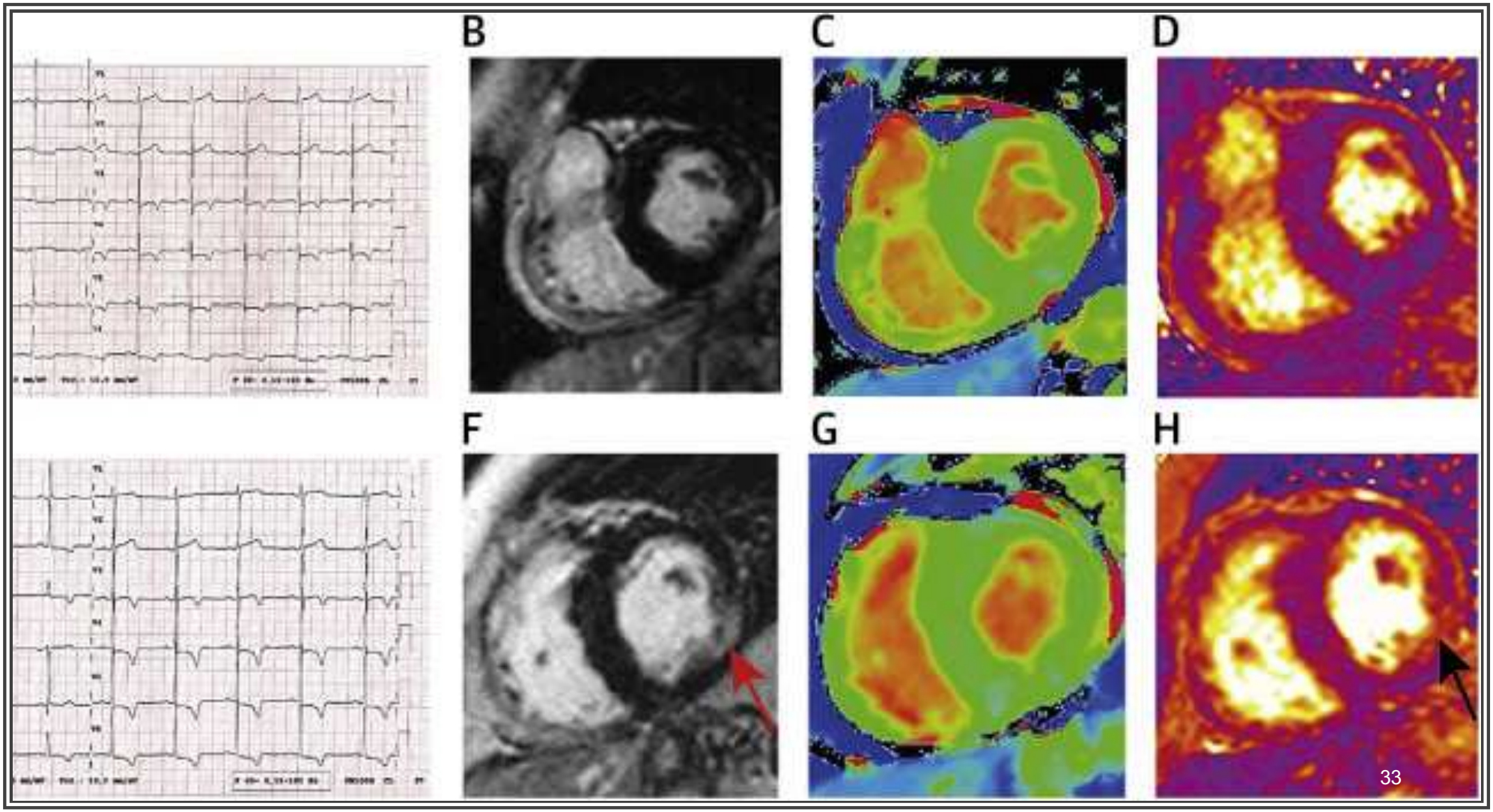
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Summary

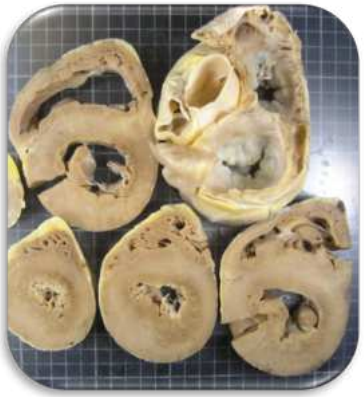
Fabry Disease Cardiomyopathy

- Cardiomyopathy associated with Fabry Disease manifests mainly as LVH
- Glycosphingolipid accumulation and inflammation / immune activation
- Cardiac MRI is essential for diagnosis and staging
- Early treatment can improve clinical outcomes

#3

Special Cardiomyopathies:
Focus on the diagnosis of **Amyloidosis**

Francois Tournoux MD PhD
Director, AmyloCHUM program, Centre Hospitalier de l'Université de Montréal
Associate Professor, University of Montreal
President, Quebec Heart Failure Society
Researcher at Fonds de Recherche du Québec - Santé

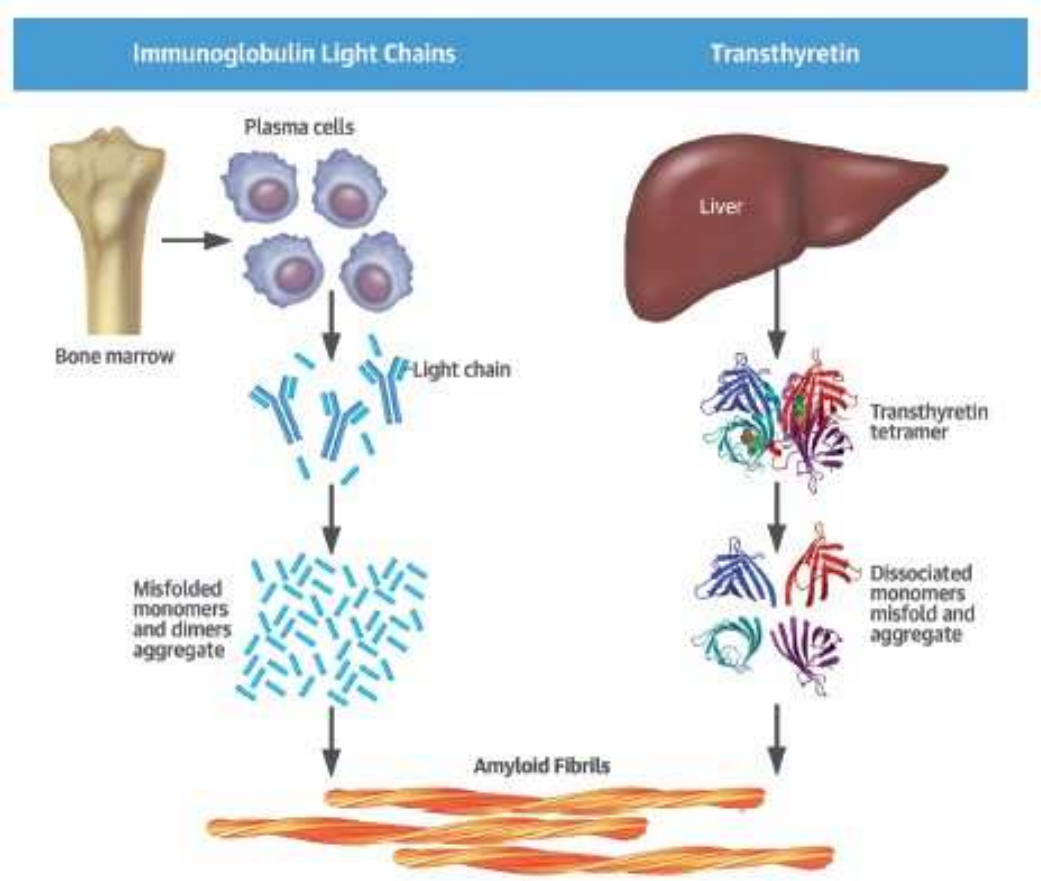


Courtesy of T Damy

Physiopathology

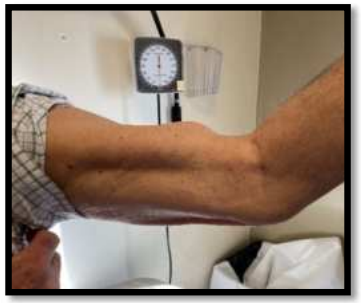
- >100 proteins ➡ amyloidosis

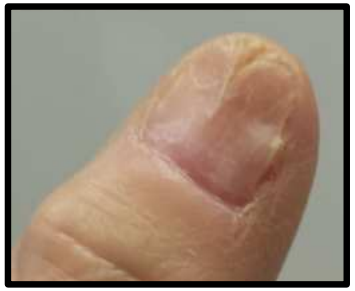
ACQUIRED	HEREDITARY
wtTTR *Wild Type Transthyretin*	**mTTR** *Transthyretin mutation*
AL *Light Chains*	**Fibrinogen**
AA *Inflammatory diseases*	**Gelsolin**
	ApoA1
	ApoA2
	Lysozyme
	Cystatin C

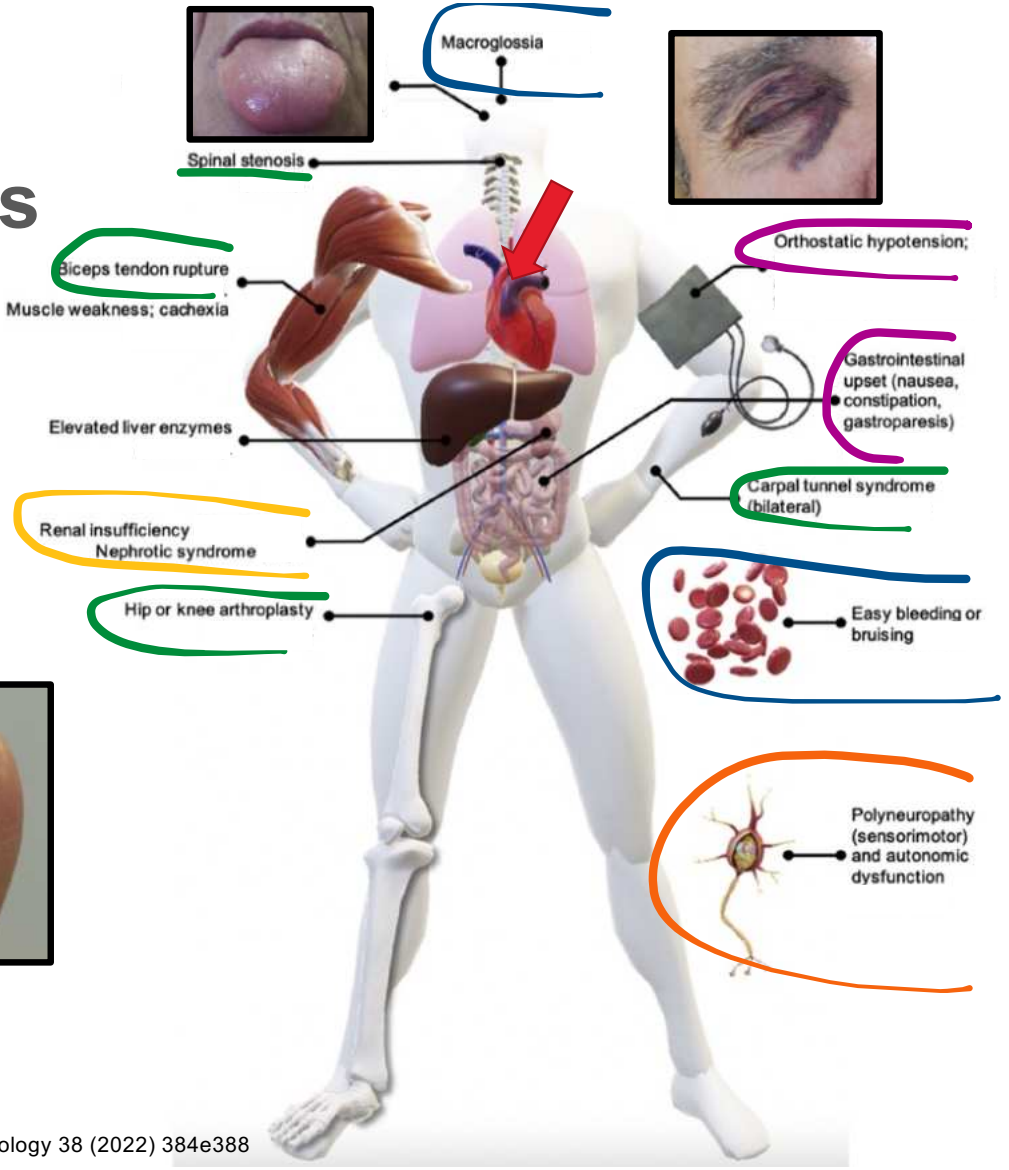


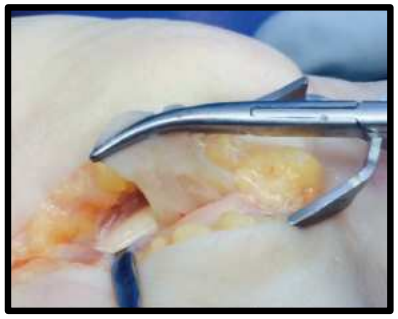
Sperry, B.W., Reyes B.A., Ikram A. and al. JACC 2018;72(17):2040-50

Clinical manifestations





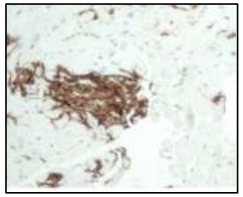




Adapted from Music S and Coll. Canadian Journal of Cardiology 38 (2022) 384e388

Cardiac manifestations

Myocardium

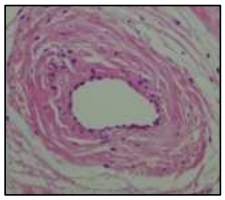


Hypertrophy
Ventricular dysfunction

Endocardium

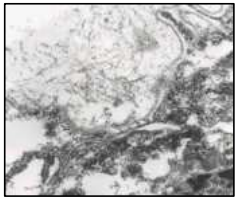
Valvular disease

Vascular



Ischemia

Pericardium



Pericardial effusion

Conduction system

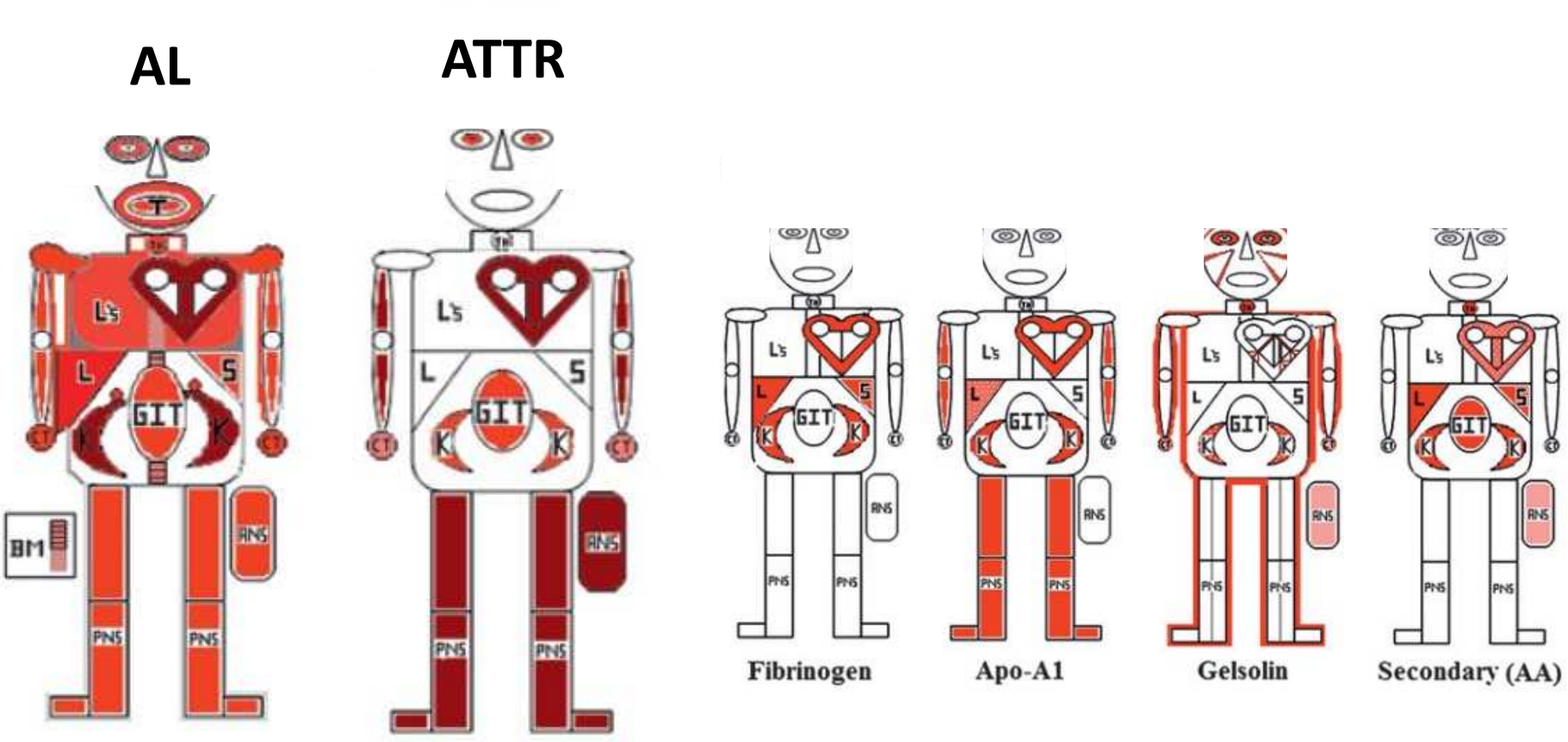
AV block

Courtesy of T Damy, adapted from Merlini, NEJM 2003

Question:

What will determine a patient's phenotype at diagnosis?

1) The form of amyloidosis: ATTR vs AL vs AA…
2) The gene mutation, in hereditary forms
3) The time when the patient is assessed
4) All of the above



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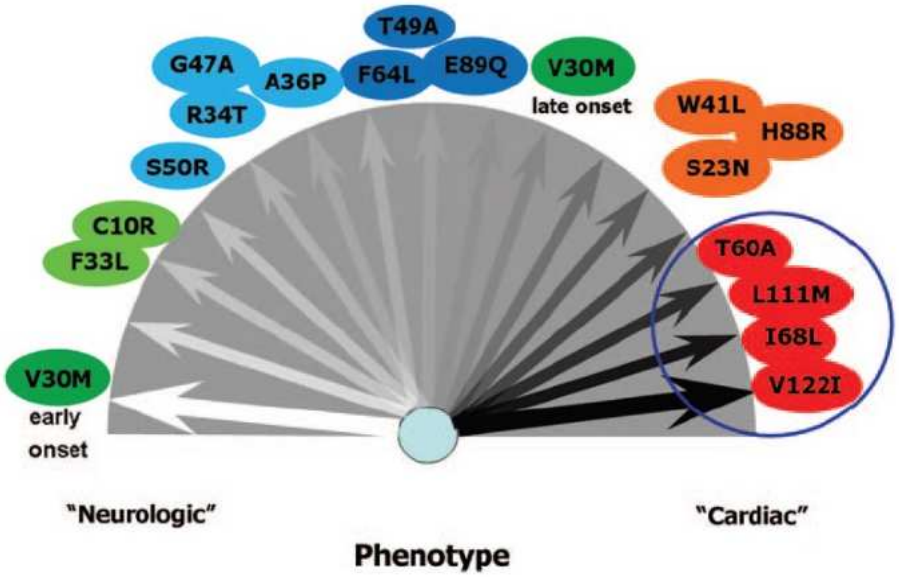
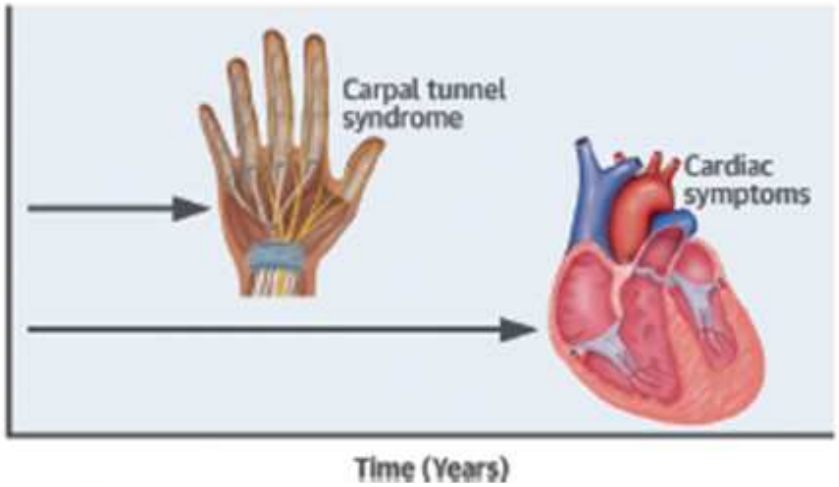
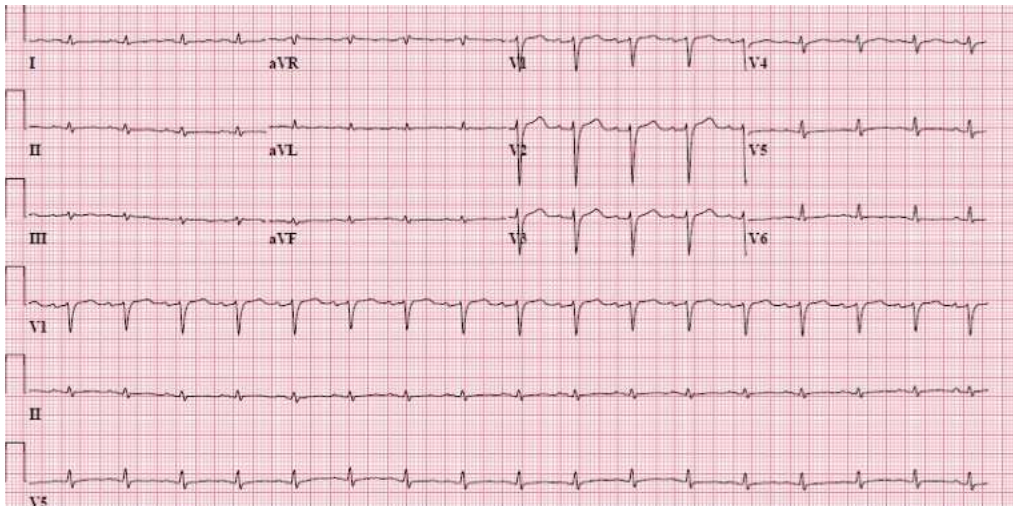




Rapezzi C. Arbustini E. Caforio A.L.P. and al. Eur Heart J 2013 May;34(19):1448-58
Sperry, B.W., Reyes B.A., Ikram A. and al. JACC 2018;72(17):2040-50

When to suspect the diagnosis?

ECG: **low QRS voltage / pseudo q waves**



≤50% of cases with ATTR-CM

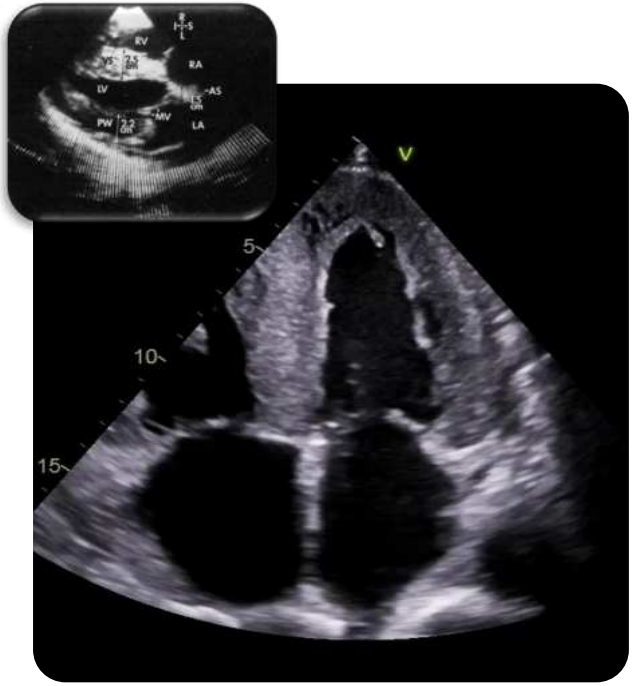
LABS:

Troponin – NTproBNP

ECHOCARDIOGRAPHY

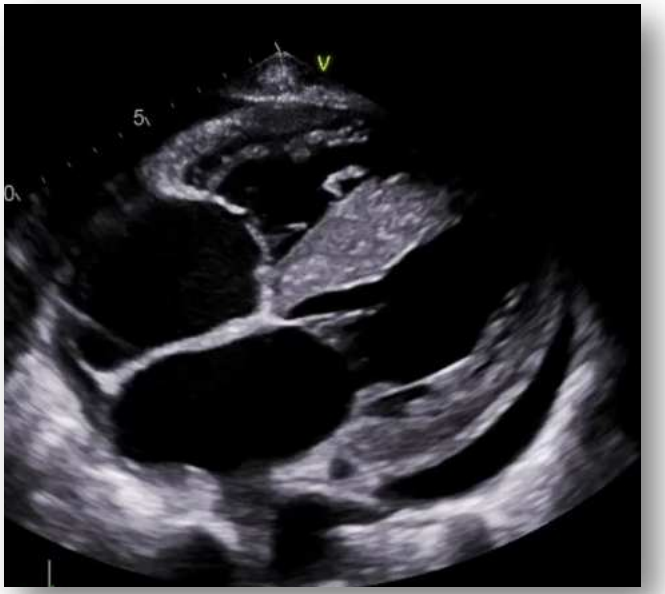
M-mode and Two-dimensional Echocardiographic Features in Cardiac Amyloidosis

ARISTARCO G. SIQUEIRA-FILHO, M.D., CLAUDIO L. P. CUNHA, M.D., ABDUL J. TAJIK, M.D., JAMES B. SEWARD, M.D., THOMAS T. SCHATTENBERG, M.D., AND EMILIO R. GIULIANI, M.D.

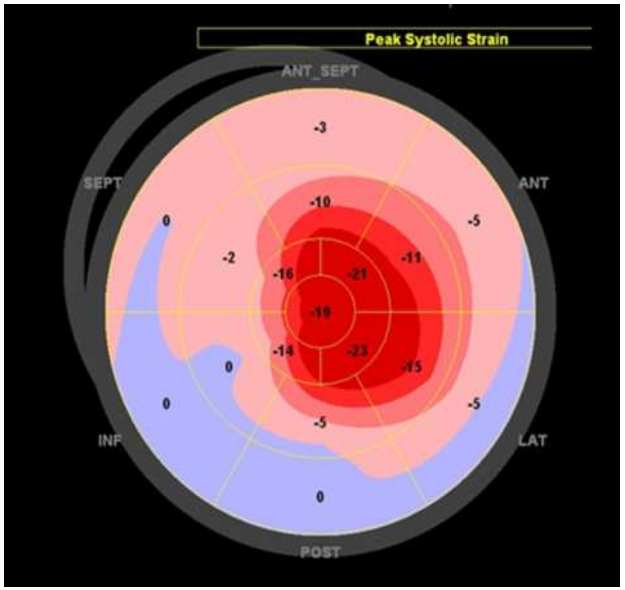


Circulation 63, No. 1, 1981

Biventricular hypertrophy

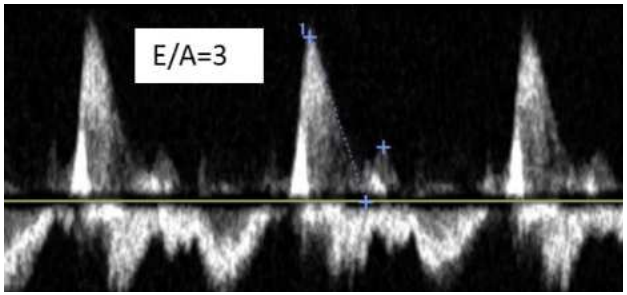


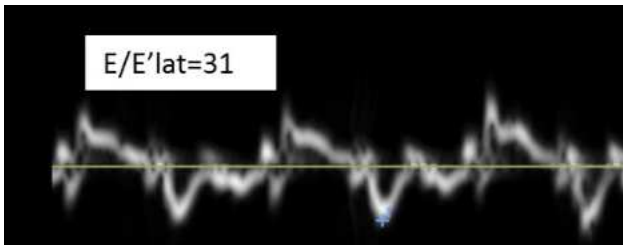
Apical sparing



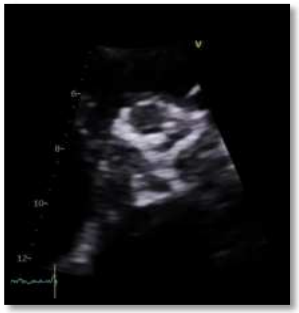
Phelan D. Heart 2012

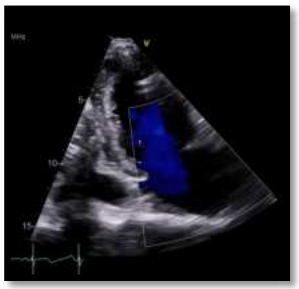
Diastolic dysfunction



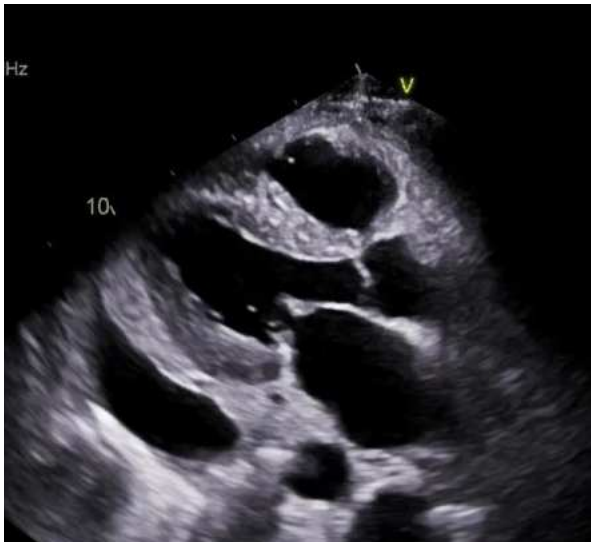


Valvular disease



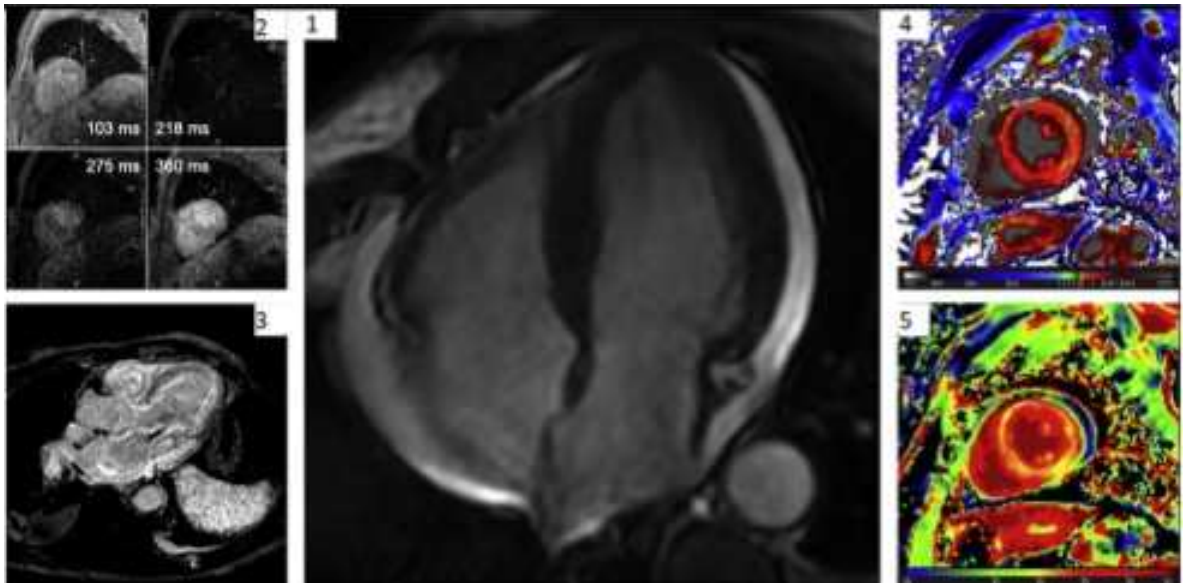


Pericardial effusion



Quarta CC et Coll. Circulation. 2014
Ternacle J et Coll. JACC 2019

CARDIAC MRI

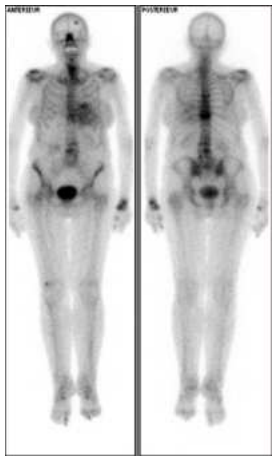


Recommendations	Class[a]	Level[b]	Ref.[c]
It is recommended that CMR studies be performed and interpreted by teams experienced in cardiac imaging and in the evaluation of heart muscle disease.	I	C	148,149
In the absence of contraindications, CMR with LGE is recommended in patients with suspected HCM who have inadequate echocardiographic windows, in order to confirm the diagnosis.	I	B	126,127
In the absence of contraindications, CMR with LGE should be considered in patients fulfilling diagnostic criteria for HCM, to assess cardiac anatomy, ventricular function, and the presence and extent of myocardial fibrosis.	IIa	B	124,126,127,130 136,138–143
CMR with LGE imaging should be considered in patients with suspected apical hypertrophy or aneurysm.	IIa	C	127,129
CMR with LGE imaging should be considered in patients with suspected cardiac amyloidosis.	IIa	C	22,147
CMR with LGE may be considered before septal alcohol ablation or myectomy, to assess the extent and distribution of hypertrophy and myocardial fibrosis.	IIb	C	150,151

Music S and Coll. Canadian Journal of Cardiology 38 (2022) 384e388

European Heart Journal (2014) 35, 2733–2779

How to confirm the diagnosis?

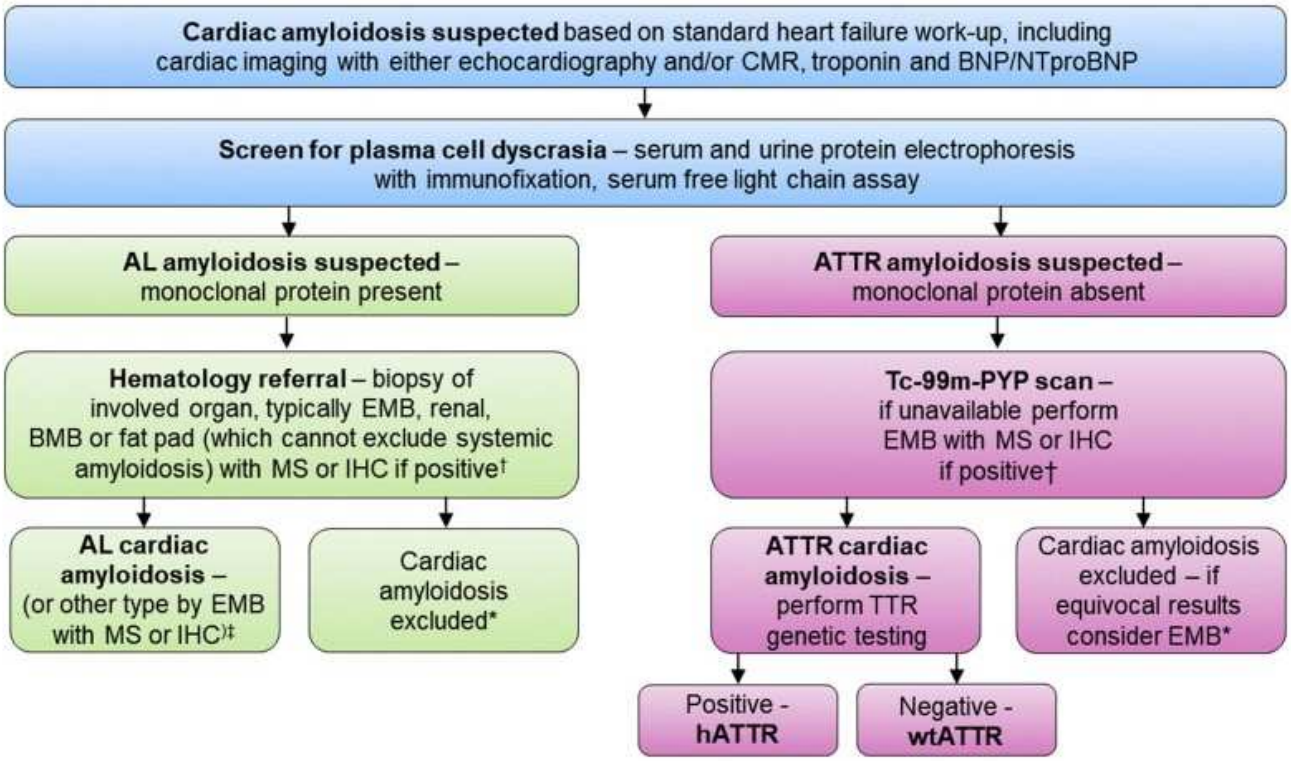


ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI Expert Consensus Recommendations for Multimodality Imaging in Cardiac Amyloidosis: Part 1 of 2—Evidence Base and Standardized Methods of Imaging

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

Grade 2 or 3 positive = **specificity and PPV >98%**

How to confirm the diagnosis?



CCS guidelines 2020 Fine N.M., Davis M.K., Anderson K. and al. CJC 2020 March;36(3):322-34

CONCLUSION

- The first step is to **look for the red flags:** physical exam, ECG, biomarkers…
- **For echocardiographers:**
  - Ask the patient for her/his medical history
  - Have a look at the ECG
  - Do not spend all your energy on the strain!
- **To confirm the diagnosis:** ask for the right exam at the right time for the right patient

Questions and Discussion