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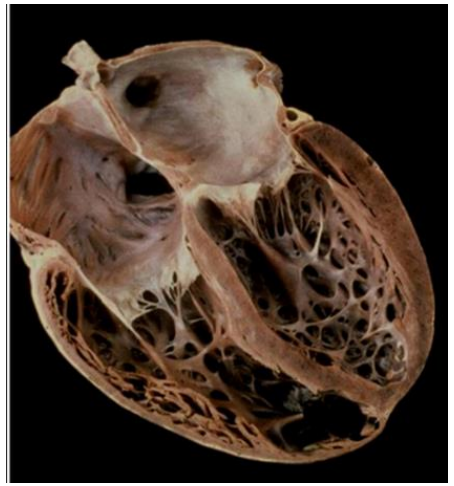
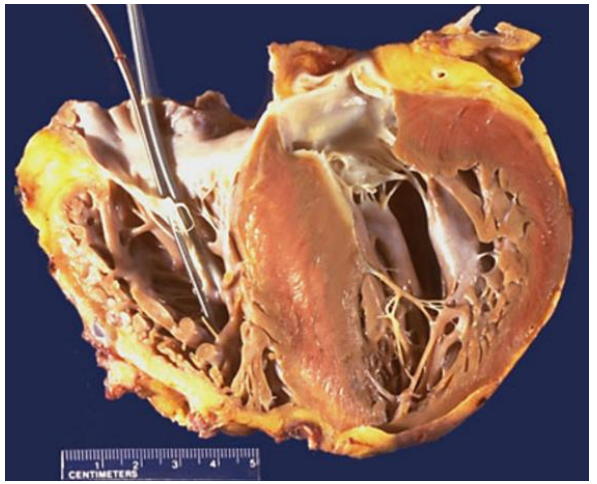
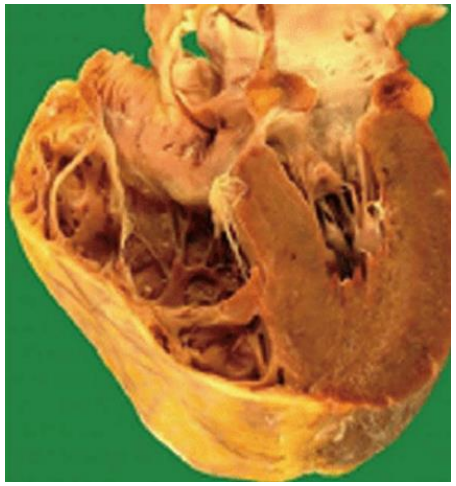
Cardiomyopathies and Genetics

Heart Failure, Swiss Webinar series der Arbeitsgruppe Herzinsuffizienz







Christiane Gruner, Cardiology, University Heart Center, Zurich

Content

1. Case No 1 – not everything that looks like dilative cardiomyopathy is a DCM

2. Case No 2 – value of EKG in the diagnostic process of cardiomyopathies

3. Case No 3 – HCM family and phenotypic expression

Classification cardiomyopathies

Primary cardiomyopathies

- Dilatative cardiomyopathy
- Hypertrophic cardiomyopathy
- Arrhythmogenic right ventricular cardiomyopathy
- Restrictive cardiomyopathy
- others: left ventricular noncompaction cardiomyopathy, arrhythmogenic cardiomyopathies

Secondary cardiomyopathies

- Ischemic cardiomyopathy
- Valvular cardiomyopathy
- Hypertensive cardiomyopathy
- Tachy-cardiomyopathies
- …

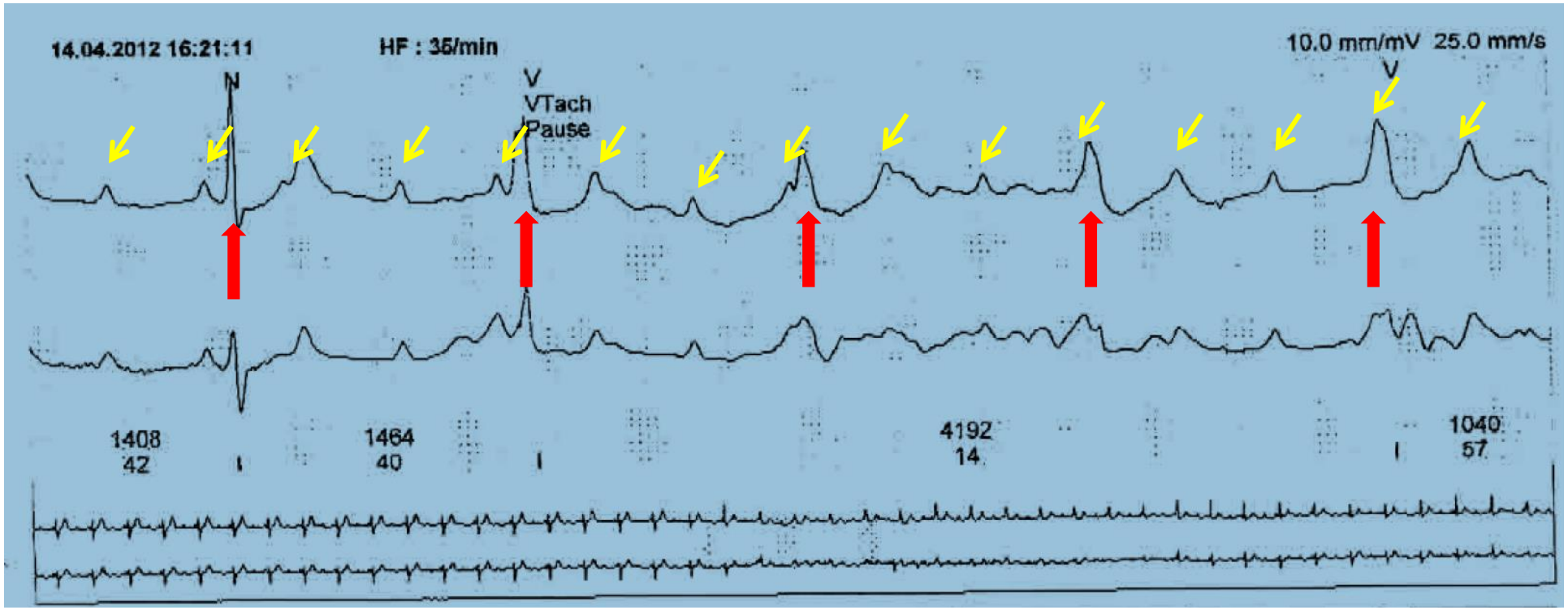
Elliott et al, EHJ 2008;29:270-76

Case No 1, history

- 63-years old female patient who was completely asymptomatic and healthy until 6 months ago
- During the past 6 months increasing symptoms with exercise intolerance, relatively low heart rate and ankle edema
- PAST MEDICAL HISTORY: unremarkable, no surgeries, no hospital stays, no chemotherapy, no radiation therapy
- SYSTEMIC REVIEW: no drugs, no alcohol, lifelong nonsmoker, unremarkable travel history
- FAMILY HISTORY: no known cardiac issues (parents, 2 siblings, 3 children)

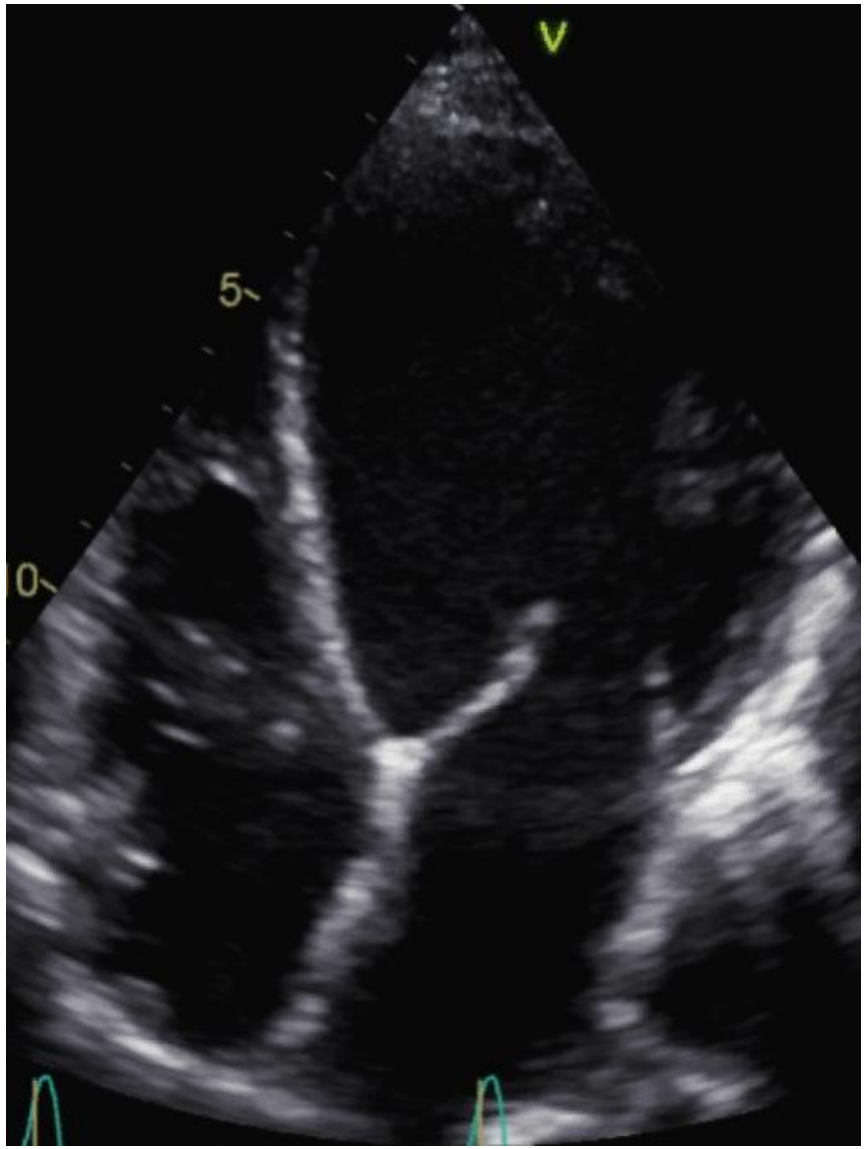
GP sent her for Holter-EKG because of relatively low heart rate

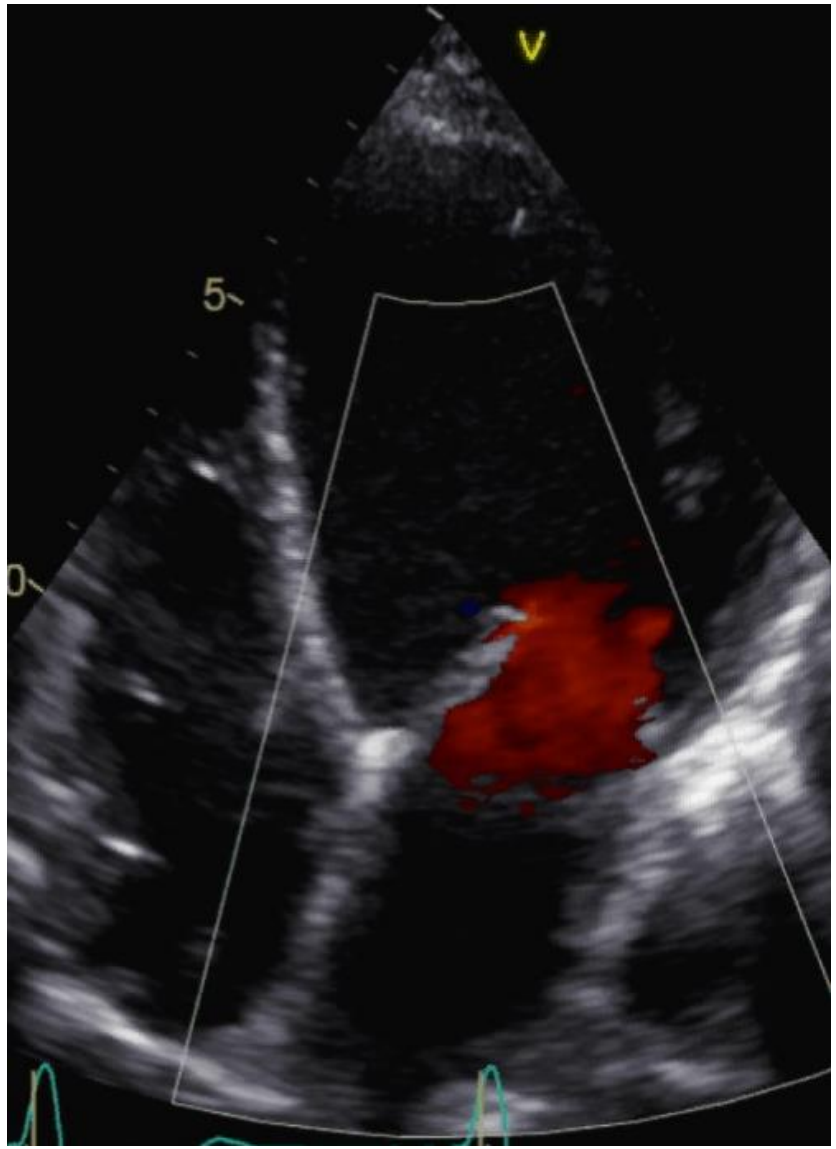
Case No 1, Holter EKG



High degree AV-Block (intermittently)

Case No 1, echocardiography

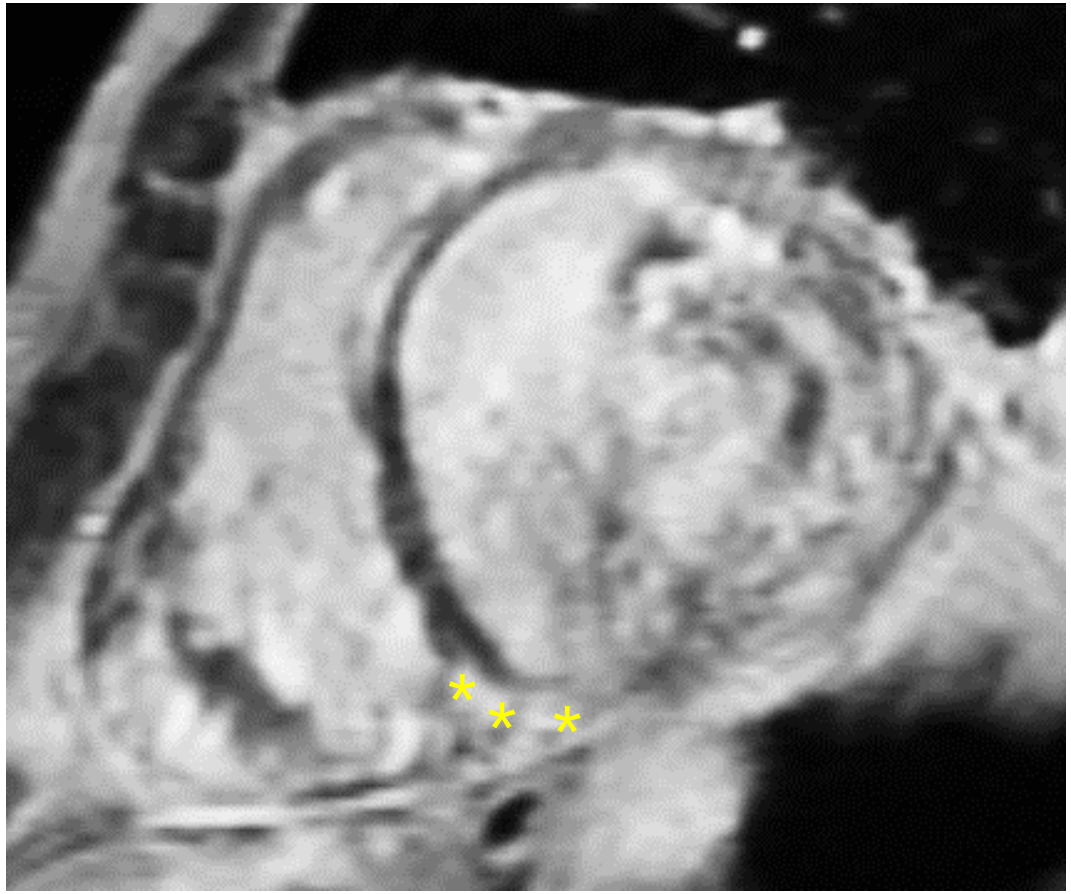




- Dilated left ventricle
- Reduced LVEF (30%)
- Moderate mitral regurgitation

Case No 1, further diagnostics

- CORONARY ANGIOGRAM: normal coronary arteries, LVEDP 17mmHg
- CARDIAC MRI: LGE images with significantly reduced quality, suspected mid wall fibrosis inferior and inferior-lateral



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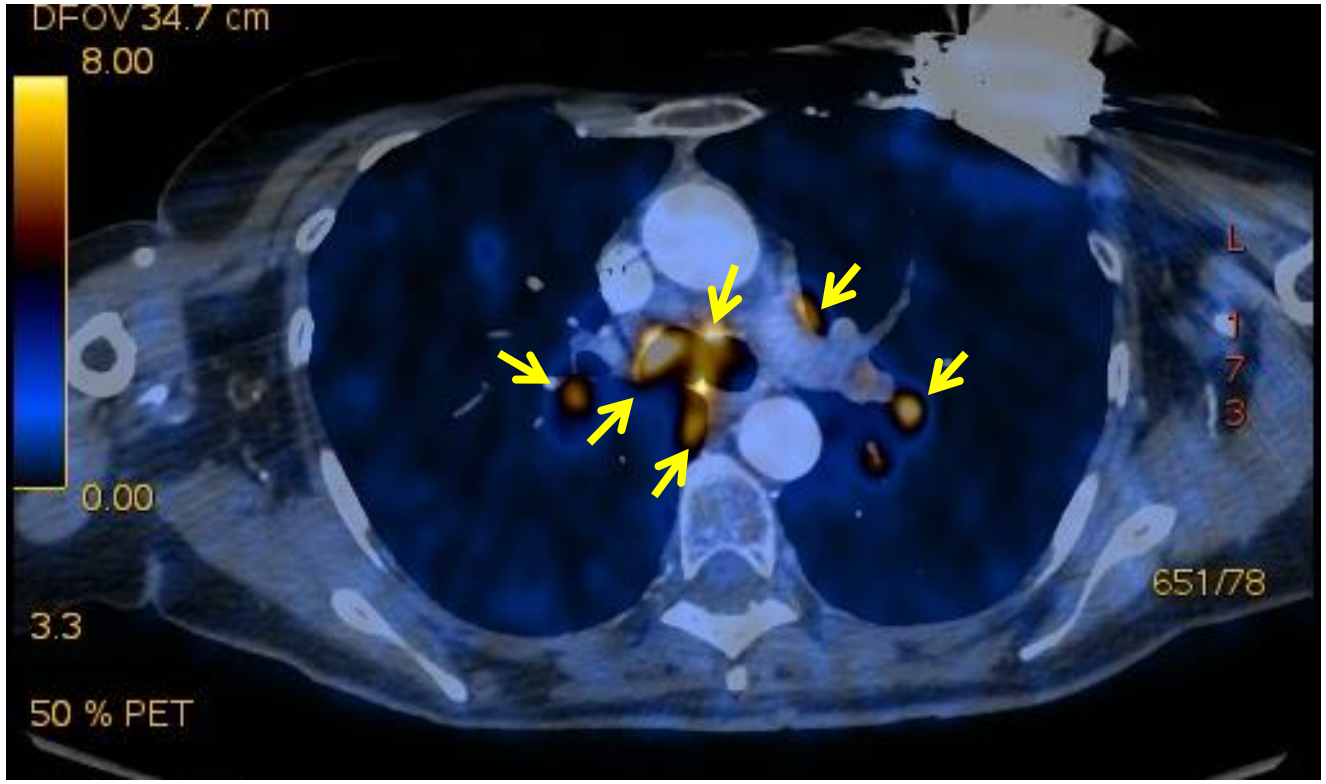
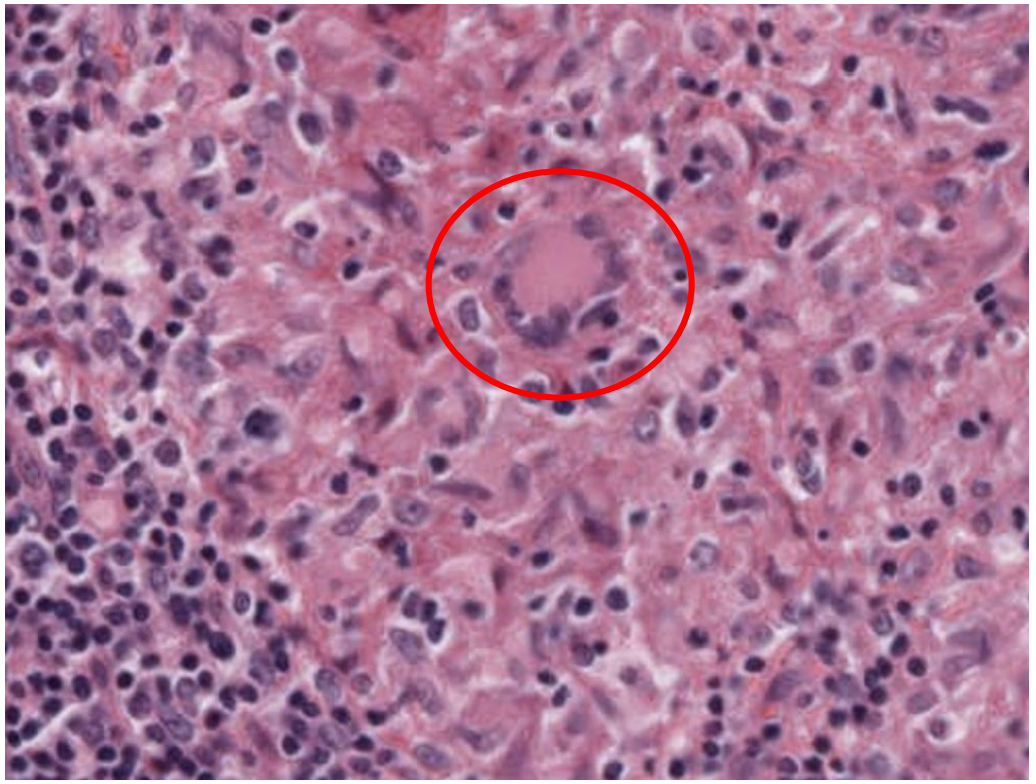
Case No 1, further diagnostics



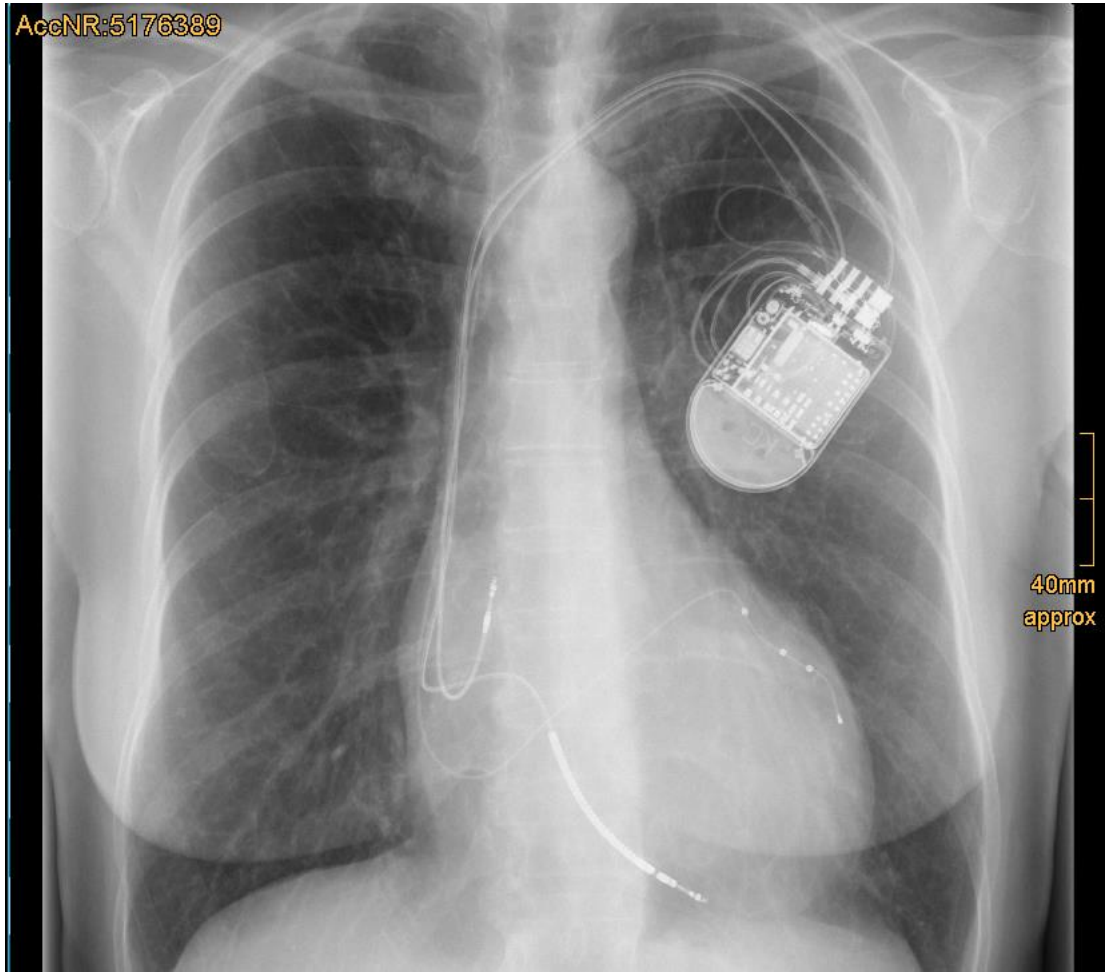
FDG-PET: bilateral lymphadenopathy



TRANSBRONCHIAL BIOPSY

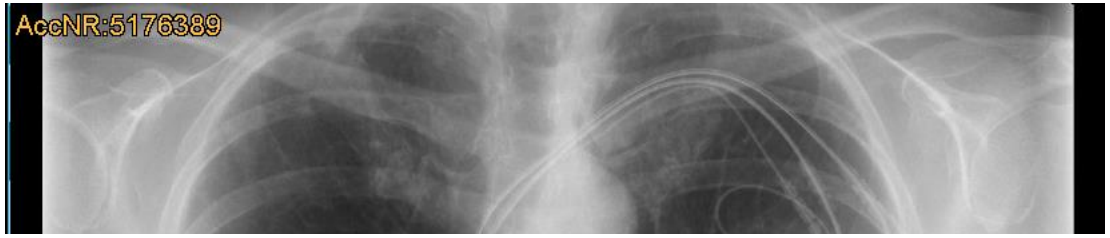
Sarcoidosis with cardiac and pulmonary involvement

Case No 1, treatment



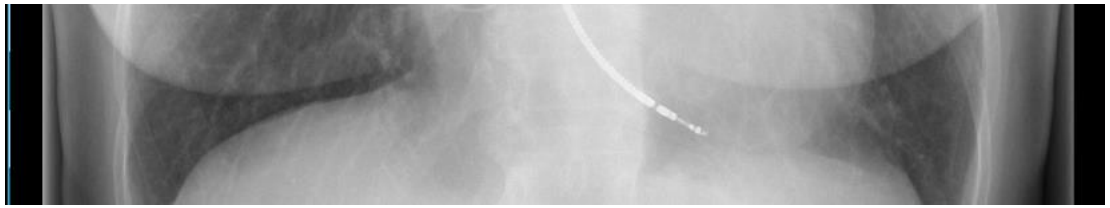
- Patient received CRT-D
- Heart failure medication (ACE-I, BB, diuretics)
- Immunsuppressive agents (steroids + MMF, later adalimumab)
- Ejection fraction improved to 45-50%, patient is asymptomatic

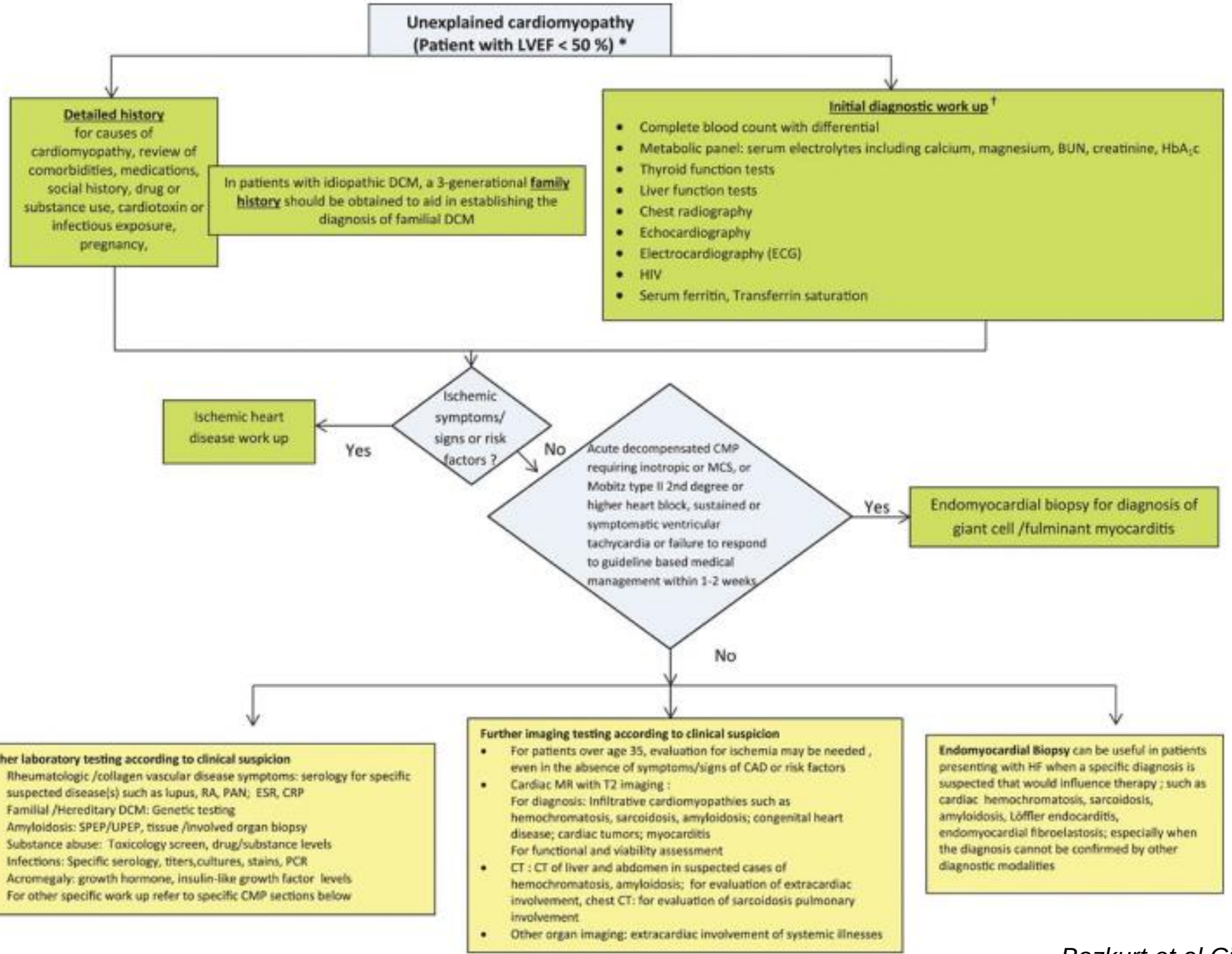
Case No 1, treatment



TAKE HOME MESSAGE # 1:

CORRECT DIAGNOSIS IS KEY AND HAS IMPLICATIONS ON TREATMENT, PROGNOSIS AND THE FAMILY!!!





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Bozkurt et al,Circulation 2016;134

Differential diagnosis: dilative cardiomyopathy

Coronary artery disease

Infectious/inflammatory

- viral myocarditis
- giant cell myocarditis
- HIV, Hepatitis B/C
- Chagas

Metabolic

- Hypo-, Hyperthyreoidosis
- Diabetes mellitus
- Obesity
- Mitochondrial cytopathies (Barth-S.,..)
- Acromegaly

Toxic

- Alcohol
- Chemotherapy
- Radiation
- Metamphetamines
- Methylphenidate

Pregnancy

- Peripartum cardiomyopathy

Neuromuscular

- Curschmann-Steinert
  Duchenne, Becker
- Friedreich-Ataxia

Infiltrative

- Sarcoidosis
- Amyloidosis
- Hämochromatosis

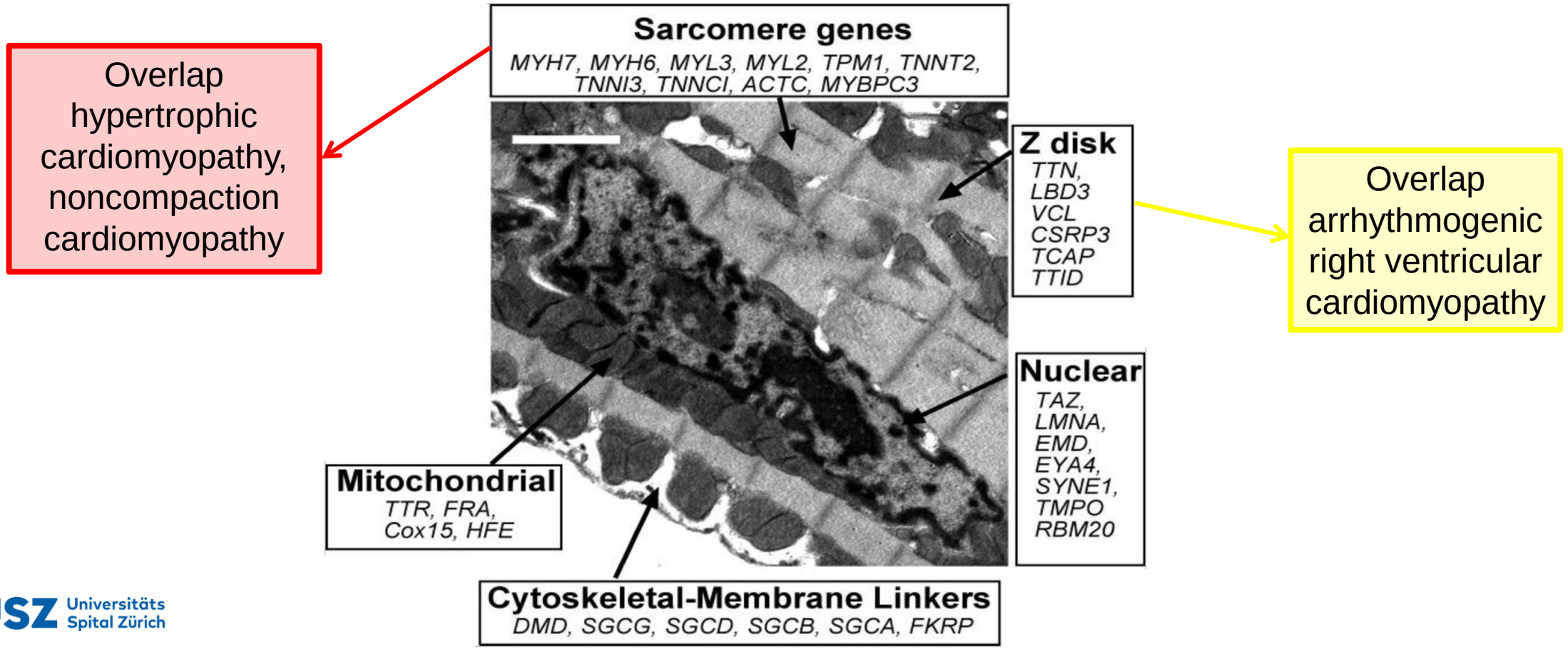
Autoimmune

- Systemic Lupus
- Rheumatoid arthritis
- Scleroderma
- Dermatomyositis
- Panarteriitis nodosa

Noncompaction CMP

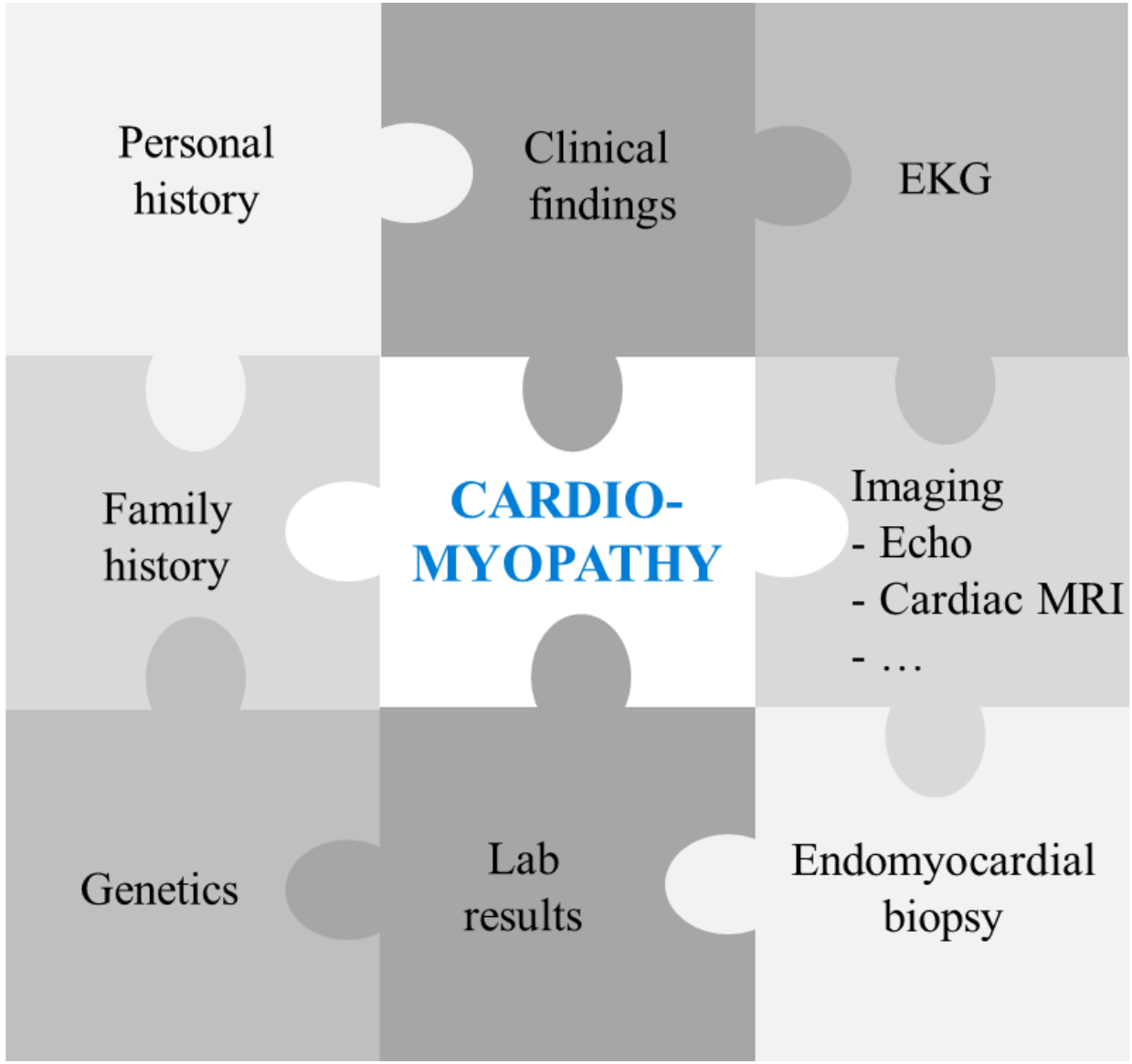
Genetics in dilative cardiomyopathy

- 1/3 of cases inherited / familial → family tree (3 generations) and family screening (EKG, TTE)
- Autosomal-dominant, X-linked, mitochondrial



Dellefave et al,Curr Op Cardiol 2010;25(3)

Cardiomyopathies, diagnostic process

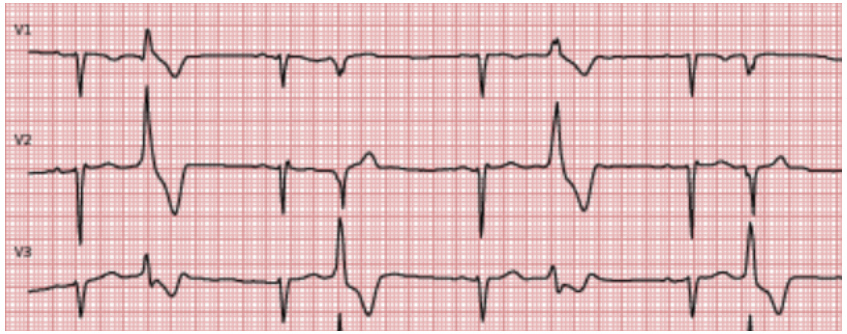


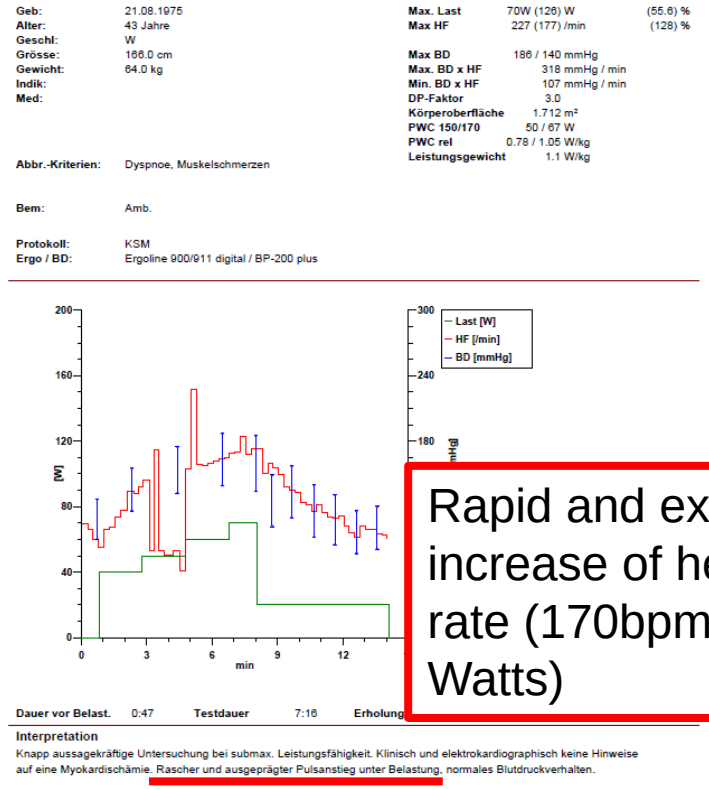
Case No 2, cardiac history

- Female patient who first felt palpitations and presyncope at the age of 35 during her second pregnancy (2010) – presented in emergency room: VPBs on monitor. In the end: **no specific measures**. Childbirth was uneventful, afterwards for several years no symptoms anymore.

- 2017 again palpitations that persisted though she quit smoking. In addition shortness of breath, leg weakness.

- October 2018 (age 43) first cardiology consult: echo normal, limited exercise capacity (70 Watts, 56% predicted), **no Holter monitor**; family history was positive for cardiac events (pacemaker, coronary artery disease, SCD). **Conclusion: lack of physical training.**

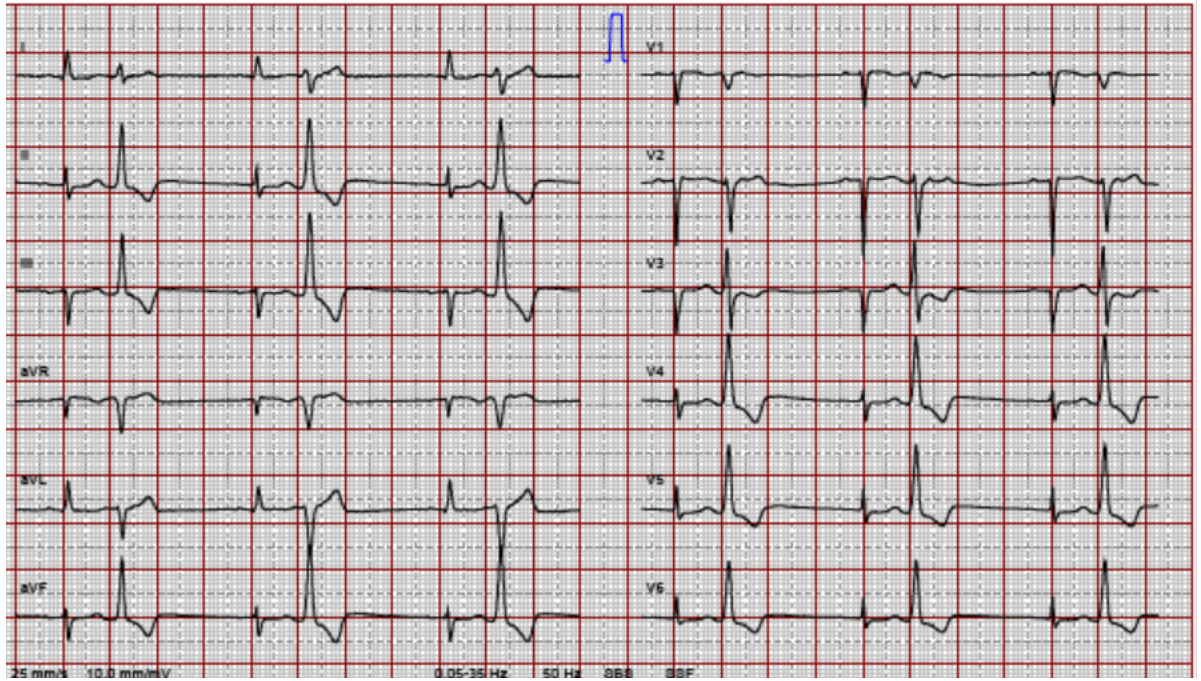


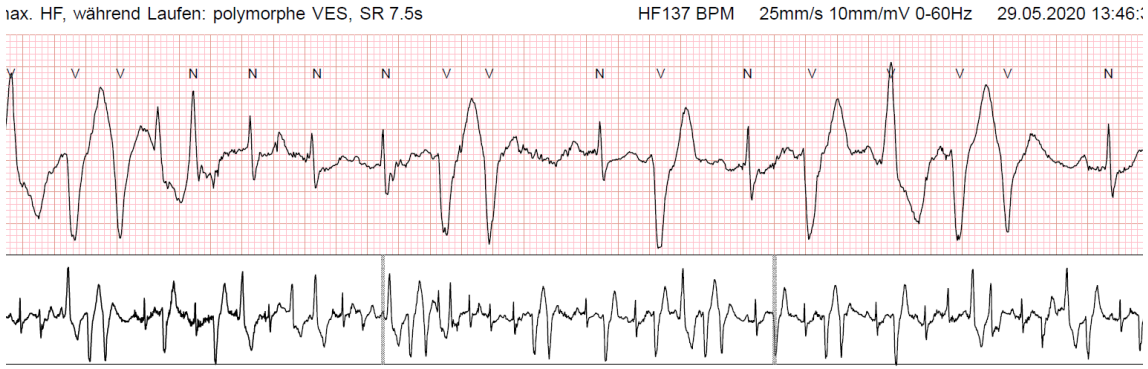


Rapid and extreme increase of heart rate (170bpm at 70 Watts)

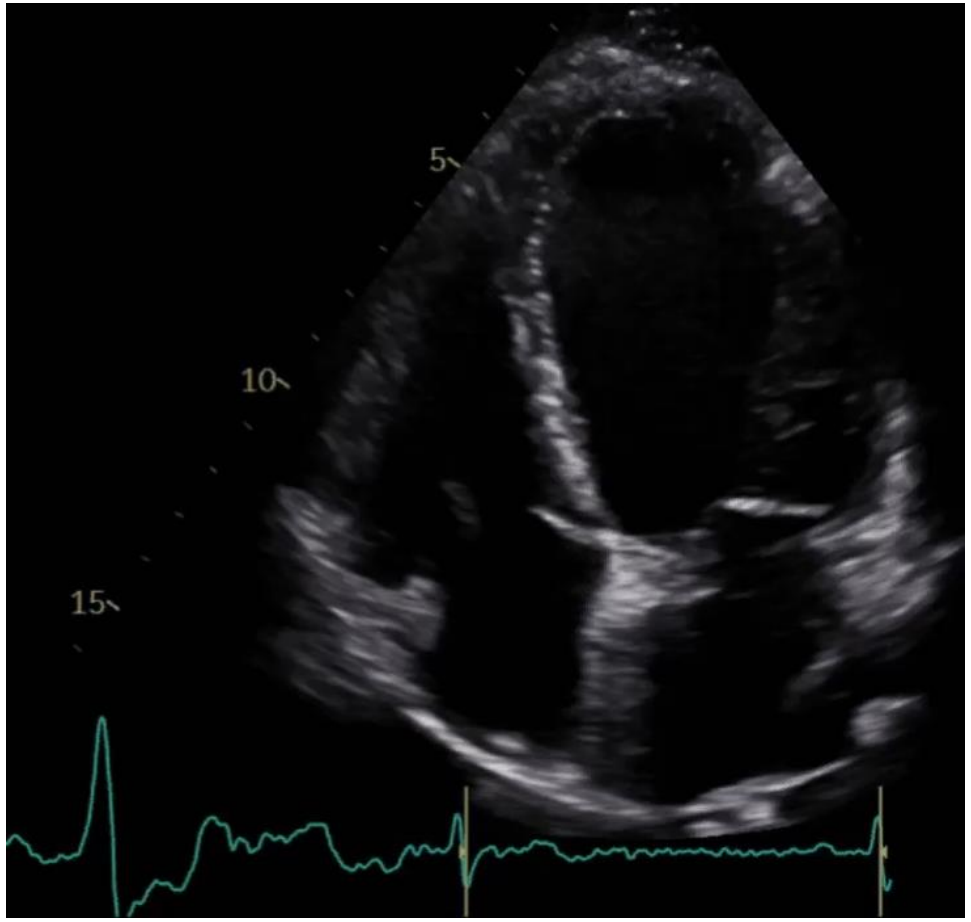
Case No 2, cardiac history

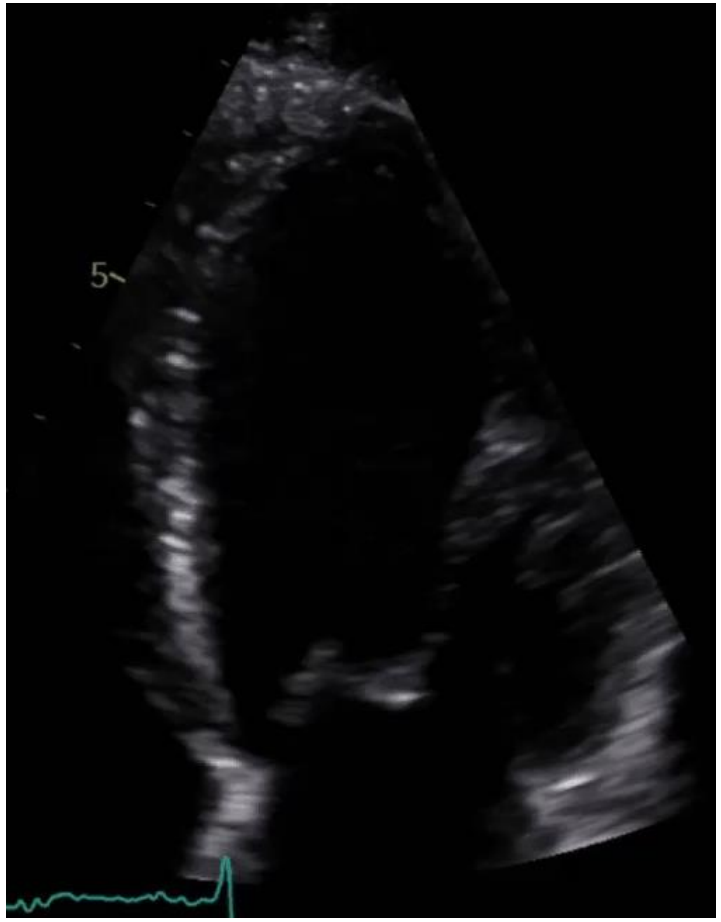
- June 2020, since 4 weeks significant palpitations, again cardiologic work-up. Echo normal, Holter monitor with frequent VPBs (36%) and nsVTs.



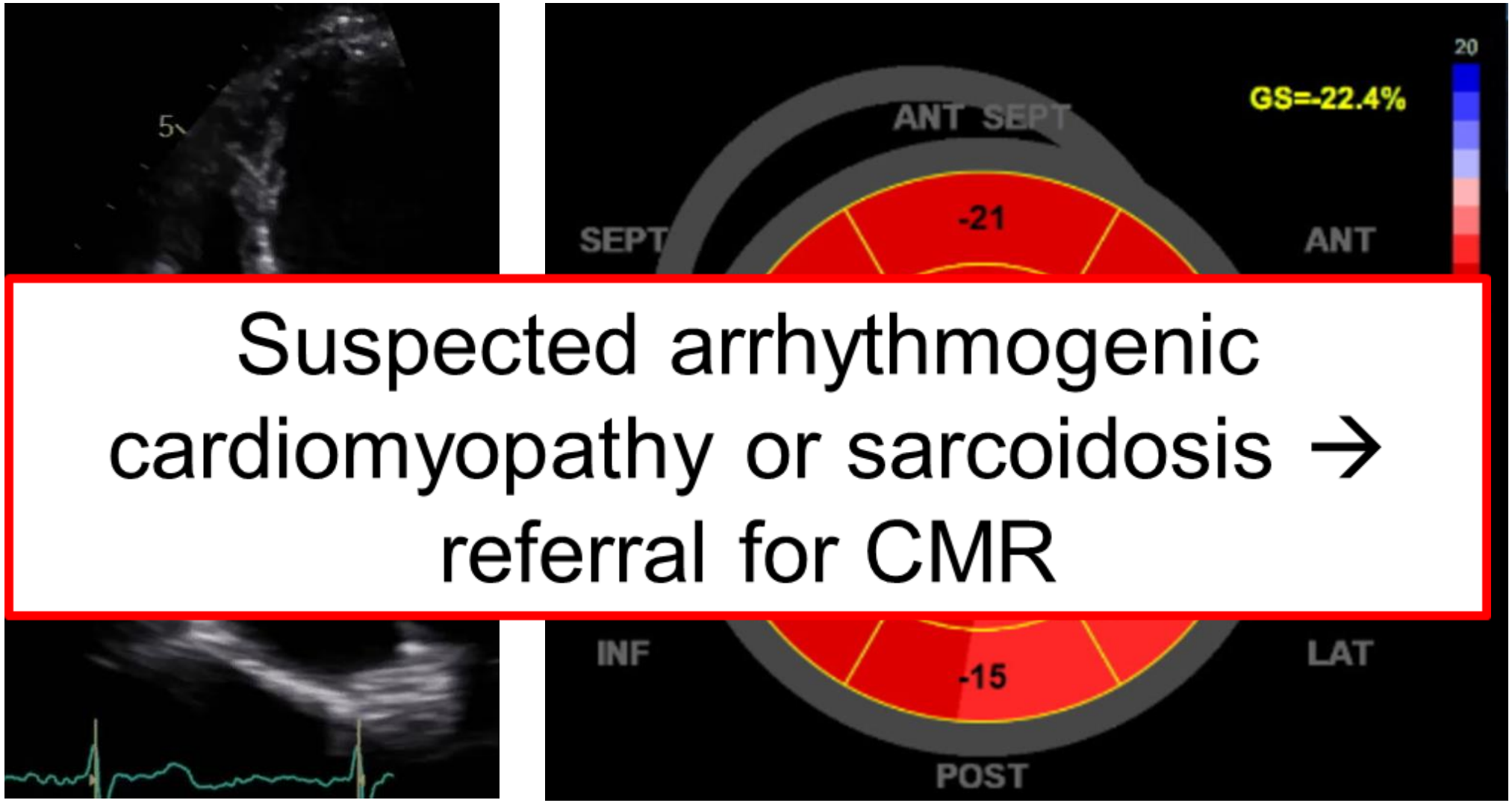


Case No 2, echocardiography



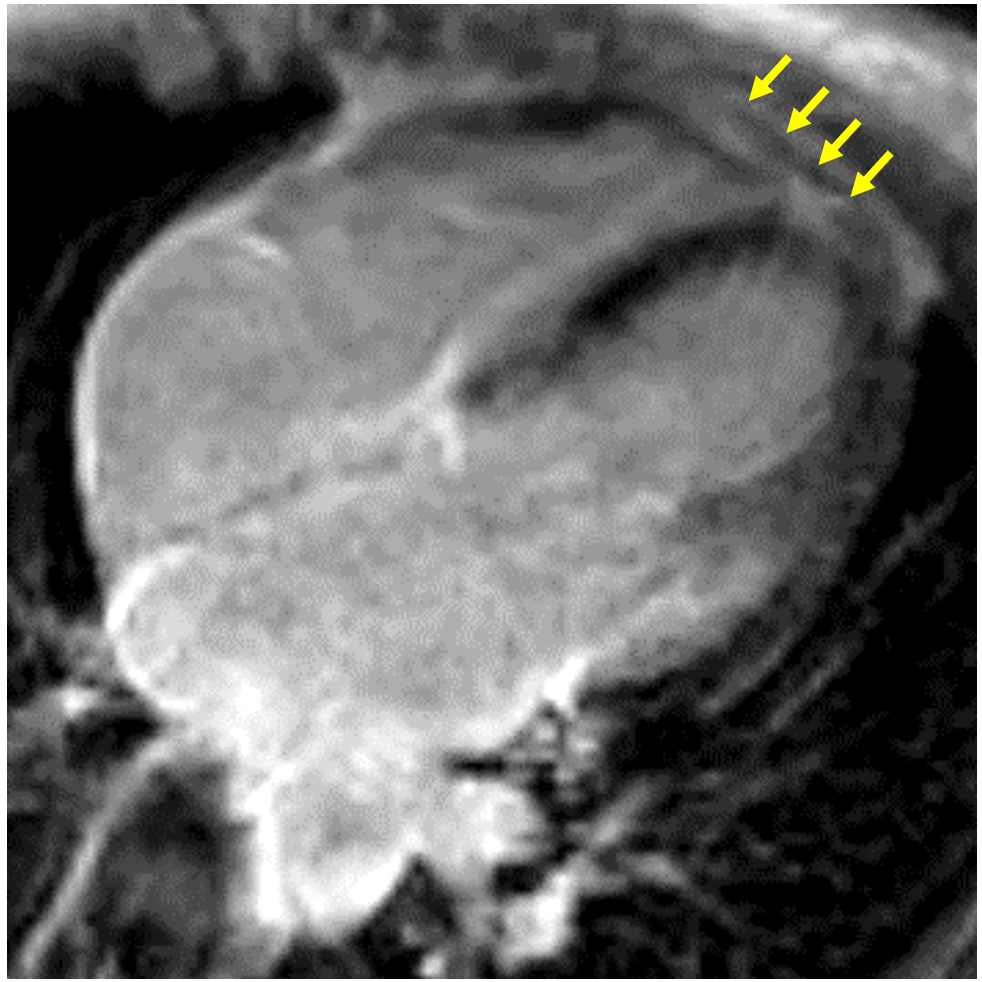


Case No 2, echocardiography



Suspected arrhythmogenic cardiomyopathy or sarcoidosis → referral for CMR

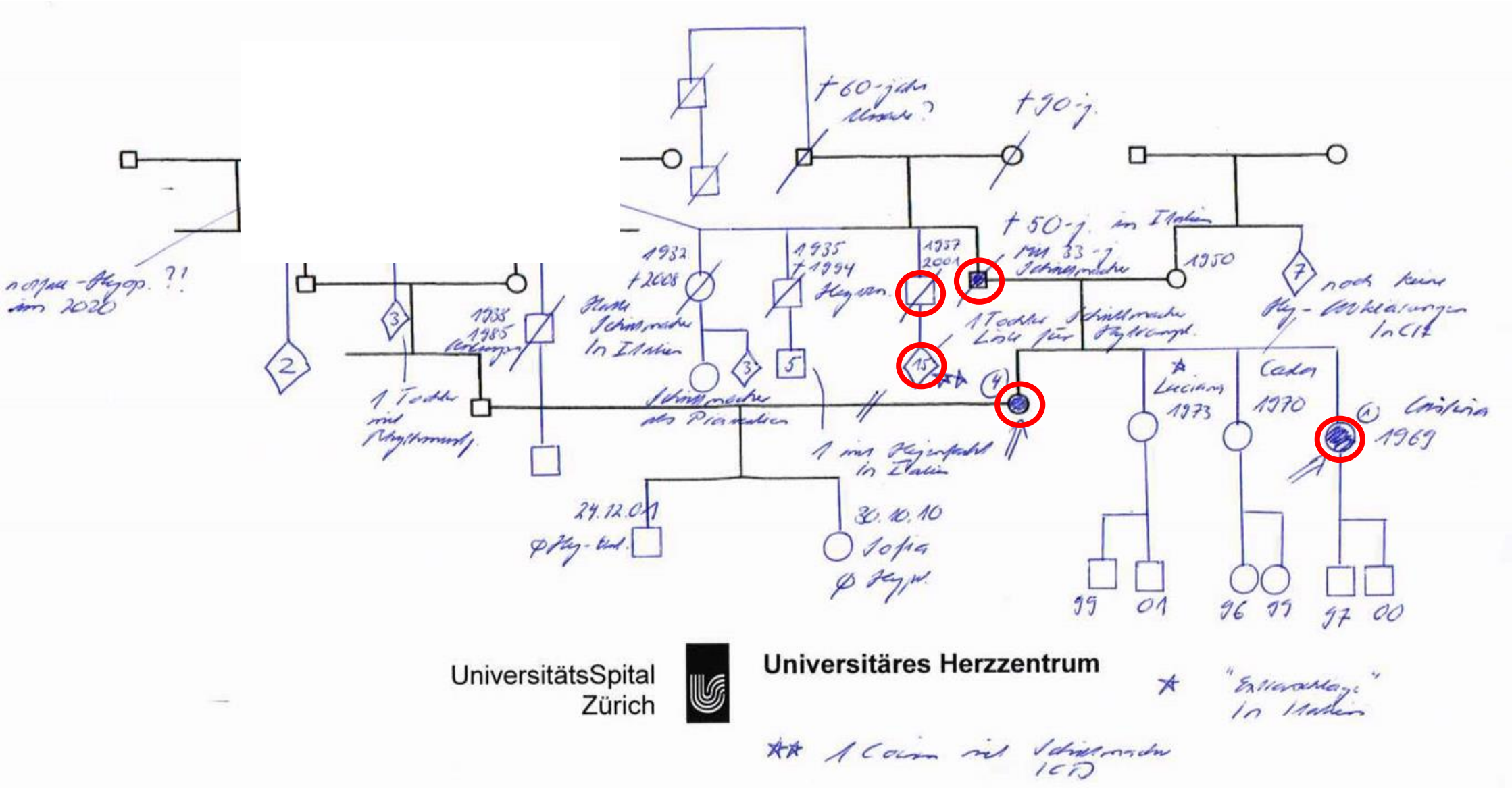
Case No 2, CMR



Conclusion: inflammatory / infiltrative process

- r/o inflammation with FDG-PET scan
- r/o coronary artery disease with CT scan

Case No 2, family history



Case No 2, genetic testing

RAPPORT D'ANALYSES MOLECULAIRES

Genève, le 21/04/2021

Indications : Suspicion de cardiomyopathie arythmogène

Demande : Séquençage de l'exome. Recherche de variants dans 151 gènes impliqués dans les cardiomyopathies (Panel: PanelApp/Cardiomyopathies_-_including_childhood_onset_v1.12,PanelApp/Cardiac_arrhythmias_v6.55, gènes verts).

Matériel analysé : ADN DM-20.1857_ADN-001

Résultat :

splice site mutation

MISE EN EVIDENCE D'UN VARIANT D'EPISSAGE DANS LE GENE *LMNA*

- site donneur d'épissage, c.356+2T>C, hétérozygote, p.?
Séq de réf: NM_170707 , chr1:156'085'067 (GRCh37/hg19)

Statut de porteur chez des apparentés:
- Soeur: [redacted] (née le 01.01.1969, DM-20.1858) **porte** le variant c.356+2T>C

Interprétation : **Le variant identifié dans le gène *LMNA* explique très probablement le tableau clinique de la patiente (variant pathogène, classe 5).**

Cardiolaminopathy / LMNA-dependent cardiomyopathy:
Form of dilated cardiomyopathy typically associated with conduction disorders and arrhythmias → ARRHYTHMOGENIC CARDIOMYOPATHY

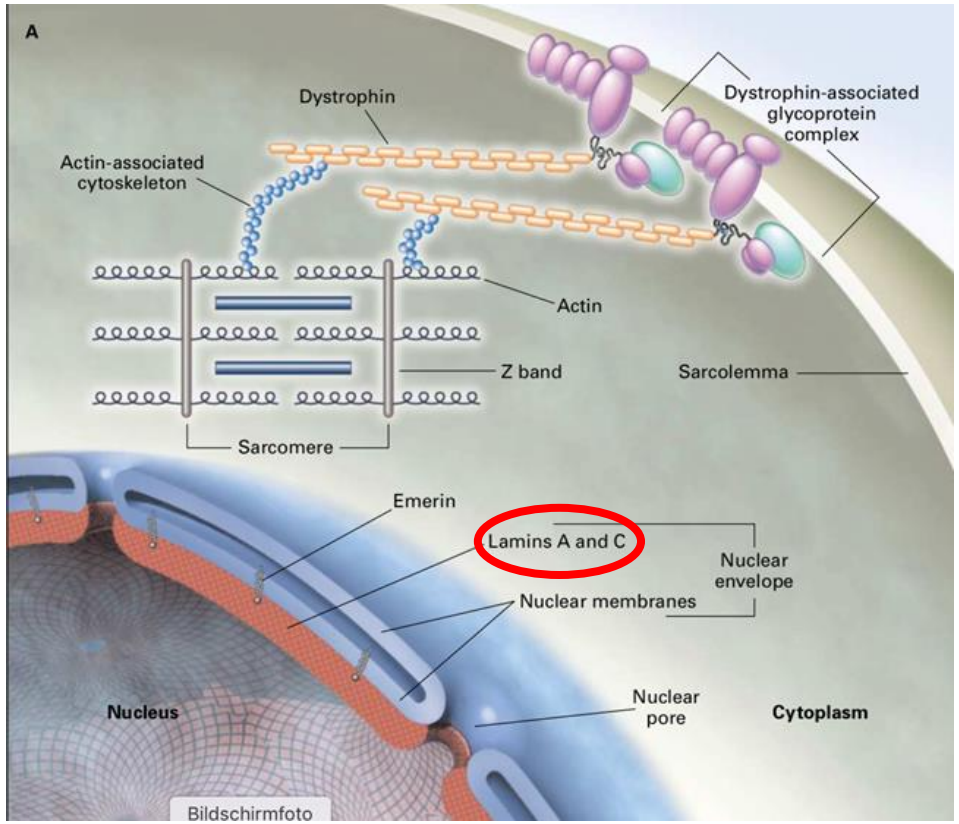
LMNA mutations – DCM described in 1999 in NEJM

MISSENSE MUTATIONS IN THE ROD DOMAIN OF THE LAMIN A/C GENE AS CAUSES OF DILATED CARDIOMYOPATHY AND CONDUCTION-SYSTEM DISEASE

DIANE FATKIN, M.D., CALUM MACRAE, M.D., TAKESHI SASAKI, M.D., MATTHEW R. WOLFF, M.D., MAURIZIO PORCU, M.D., MICHAEL FRENNEAUX, M.D., JOHN ATHERTON, M.B., B.S., HUMBERTO J. VIDAILLET, JR., M.D., SERENA SPUDICH, M.D., UMBERTO DE GIROLAMI, M.D., J.G. SEIDMAN, PH.D., AND CHRISTINE E. SEIDMAN, M.D.

Lamin A/C :

- The two main isoforms
- Component of nuclear lamina
- Determinant of nuclear structure and function
- Role in cell differentiation and tissue development



LMNA mutations – associated phenotypes

Other entities represented in this entry:

LAMIN A, INCLUDED
LAMIN C, INCLUDED; LMNC, INCLUDED
PRELAMIN A, INCLUDED
PROGERIN, INCLUDED

HGNC Approved Gene Symbol: LMNA

Cytogenetic location: 1q22 *Genomic coordinates (GRCh38): 1:156,082,572-156,140,080* (from NCBI)

Gene-Phenotype Relationships

Location	Phenotype Clinical Synopses	Phenotype MIM number	Inheritance	Phenotype mapping key
1q22	Cardiomyopathy, dilated, 1A	115200	AD	3
	Charcot-Marie-Tooth disease, type 2B1	605588	AR	3
	Emery-Dreifuss muscular dystrophy 2, autosomal dominant	181350	AD	3
	Emery-Dreifuss muscular dystrophy 3, autosomal recessive	616516	AR	3
	Heart-hand syndrome, Slovenian type	610140	AD	3
	Hutchinson-Gilford progeria	176670	AD	3
	Lipodystrophy, familial partial, type 2	151660	AD	3
	Malouf syndrome	212112	AD	3
	Mandibuloacral dysplasia	248370	AR	3
	Muscular dystrophy, congenital	613205	AD	3
	Restrictive dermopathy, lethal	275210	AR	3

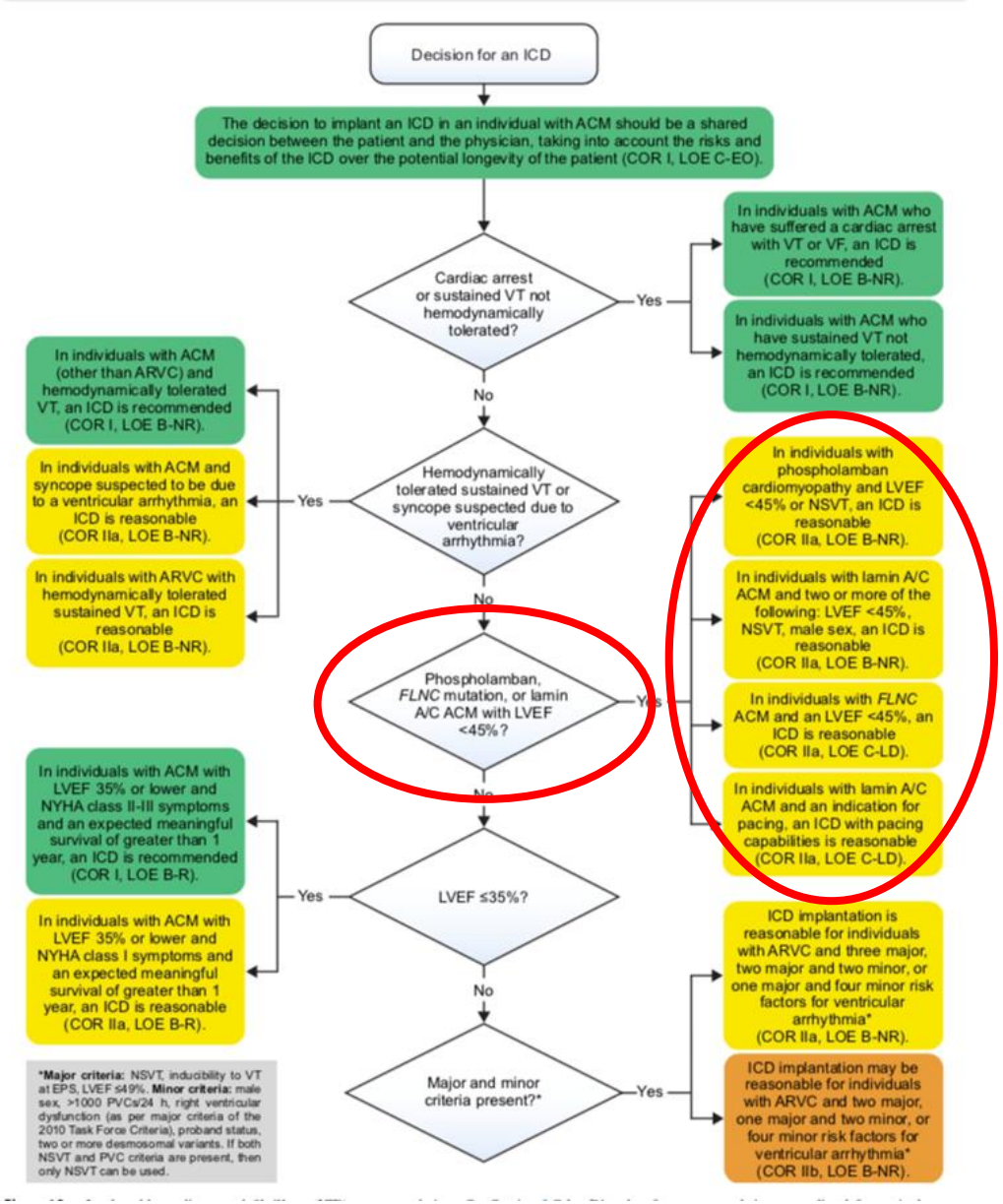
Laminopathies

Characteristics of cardiolaminopathies

- LMNA is the second most commonly mutated gene associated with familial DCM (5%), number raising up to 33% for cases presenting with both – DCM and conduction defects
- Bradyarrhythmias, supraventricular arrhythmias often precede by decades the development of DCM *(Kumar et al 2018)*
- Variable extent of ventricular dilatation, less frequently left ventricular non-compaction *(Sedaghat-Hamedani et al. 2017)*
- Very wide inter- and intrafamilial clinical variability
- Development of phenotype between 20 and 39 years of age in 2/3 of cases; complete penetrance by the age of 60
- Among DCM patients, carriers of LMNA variants experience the highest rates of SCD/VT/VF independent of LVEF *(Gigli et al. 2019)*
- Male sex, non-missense mutations and nsVTs are predictors of malignant ventricular arrhythmias

Castro et al, Frontiers in Physiology 2020

Characteristics of cardiolaminopathies



Towbin et al, Heart Rhythm 2019

Case No 2: follow-up

FU PATIENT:

- Bisoprolol 5mg od, insertion of 2 chamber defibrillator
- Neurologic work-up did not show any skelettal muscle involvement
- in the process of clinical and genetic family screening

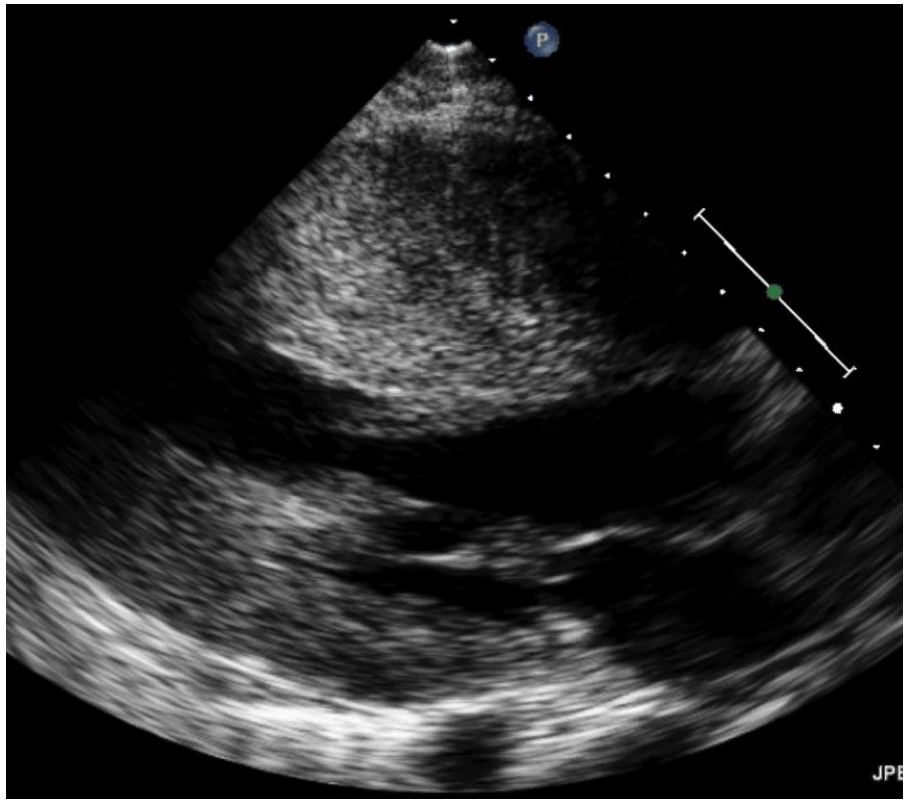
TAKE HOME MESSAGE # 2

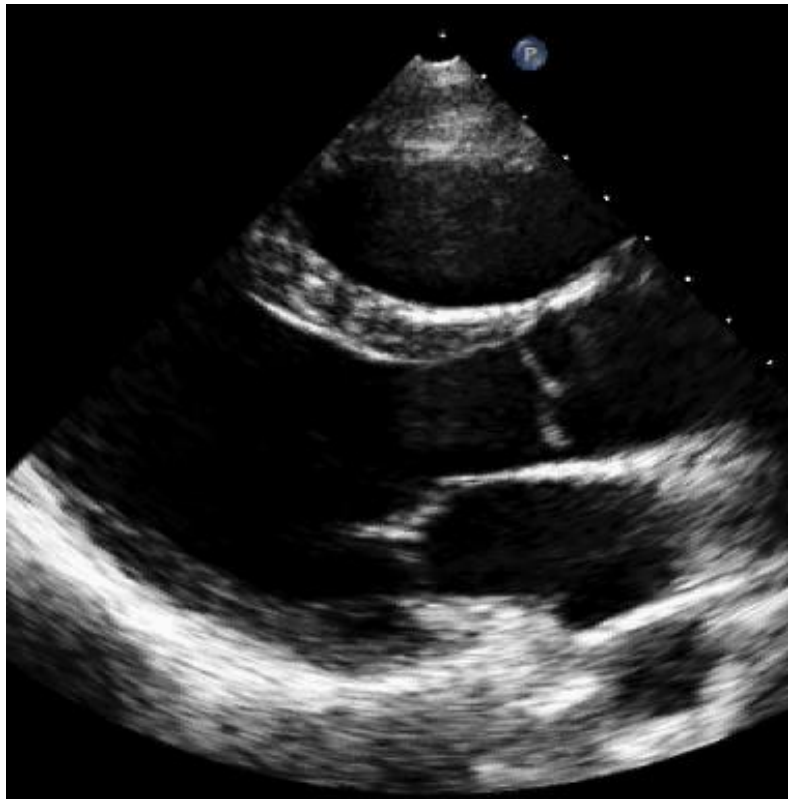
SOMETIMES THE EKG IS MORE EXCITING THAN THE ECHO

TAKE HOME MESSAGE # 3

NOT EVERY UNEXPLAINED SCAR ON CMR IS ‘POST-MYOCARDITIS’

Definition of hypertrophic cardiomyopathy





- Asymmetric left ventricular hypertrophy with maximal wall thickness of MWTH ≥15mm in the absence of LV dilatation and lack of other cardiac or systemic reasons causing left ventricular hypertrophy
- Most frequent hereditary cardiomyopathy (prevalence 1:500)

Differential diagnosis of hypertrophic cardiomyopathy

Hypertensive heart disease

Athlete's heart

Metabolic

- Fabry disease
- glycogen storage diseases
- PRKAG2 cardiomyopathy
- Danon disease
- Mucopolysaccharidosis
- Oxalosis
- Mitochondrial cytopathies
- Hypothyreoidism
- Obesity

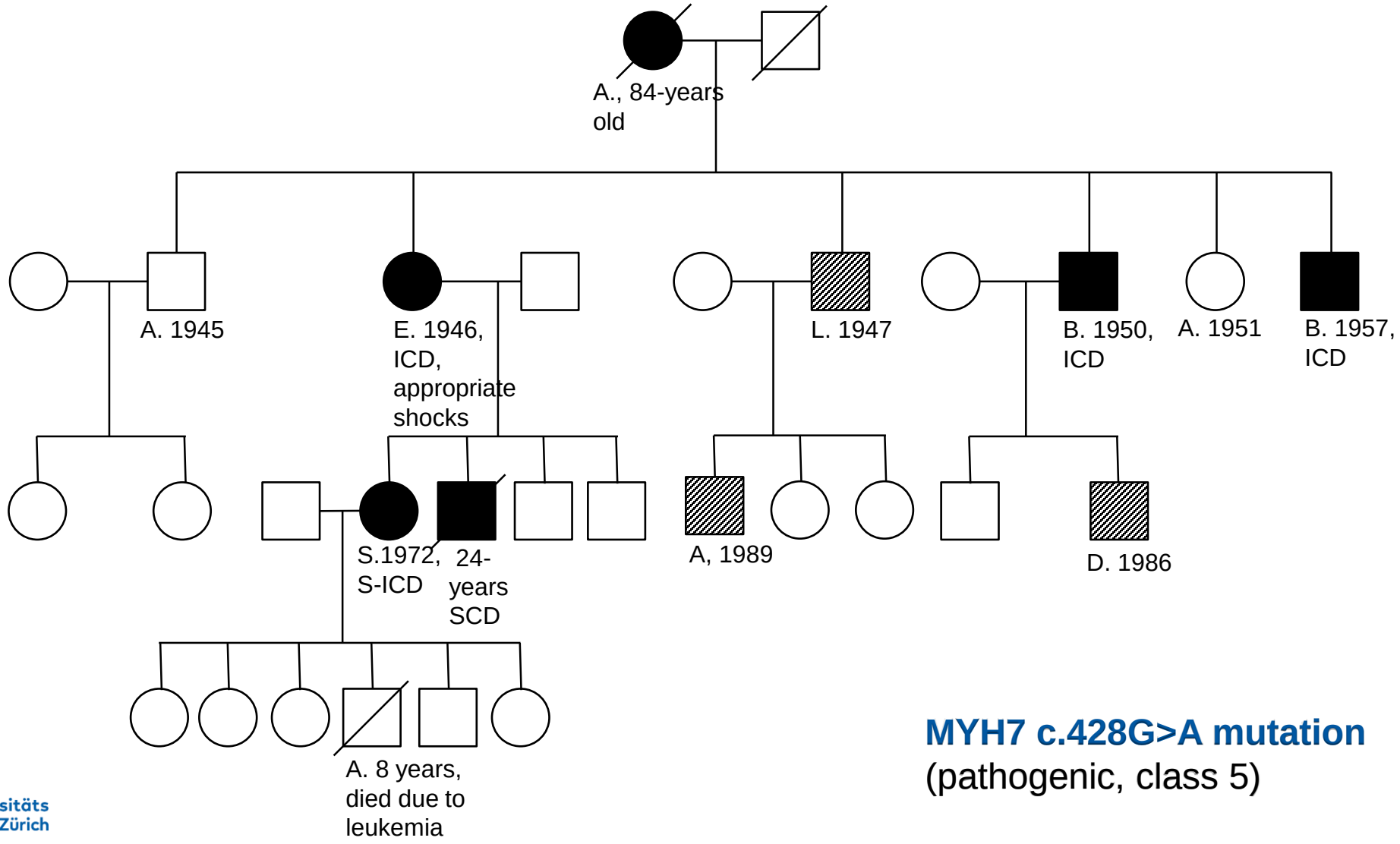
Syndromic diseases

- Friedreich ataxia
- Noonan syndrome

Infiltrative

- Amyloidosis
- Haemochromatosis
- Sarcoidosis

Case No 3, hypertrophic cardiomyopathy and phenotypic expression



MYH7 c.428G>A mutation
(pathogenic, class 5)

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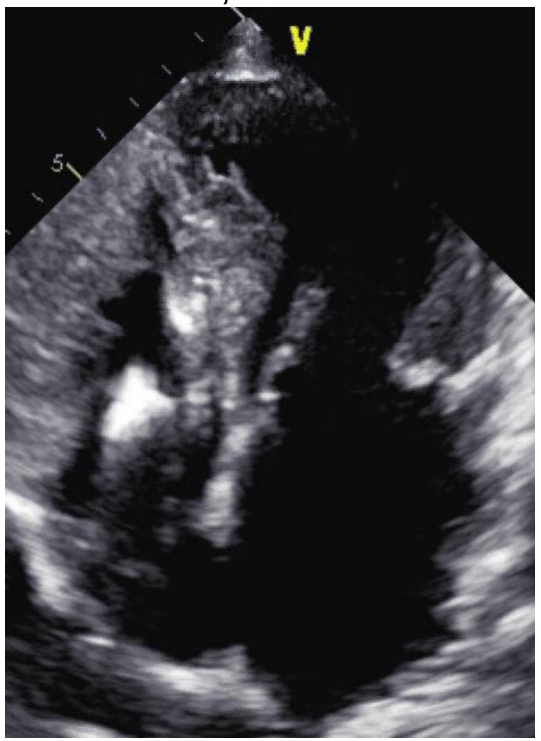
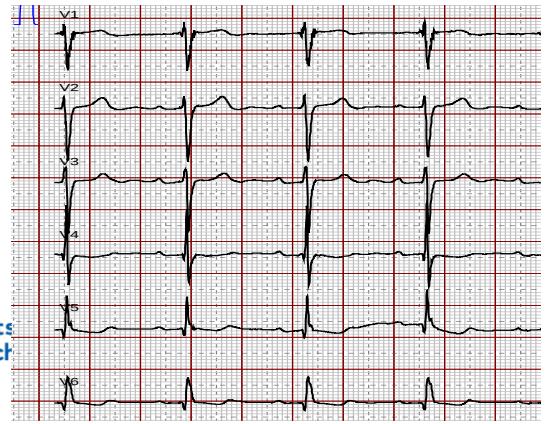
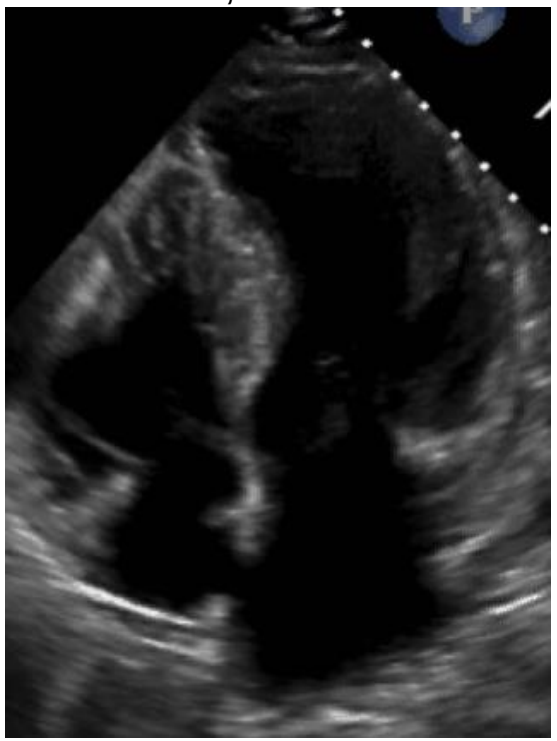
Case No 3, family members with positive geno- and phenotype

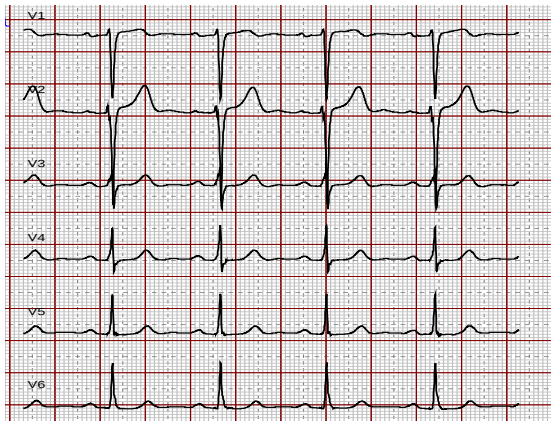
E., 1946



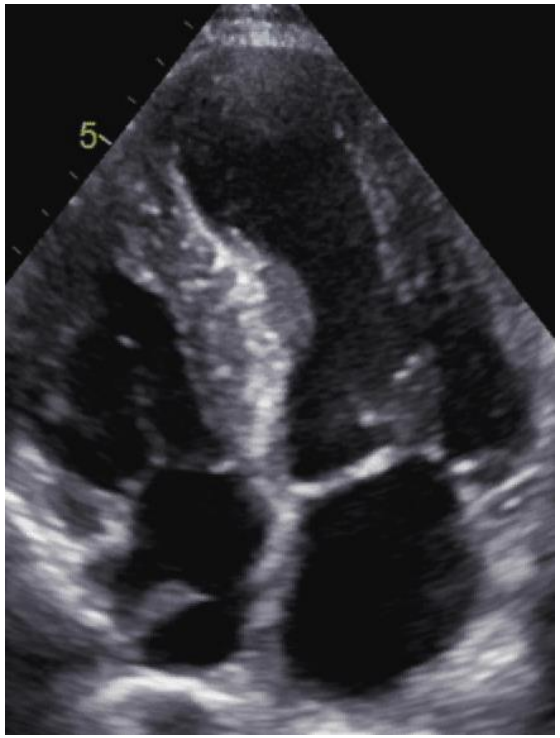


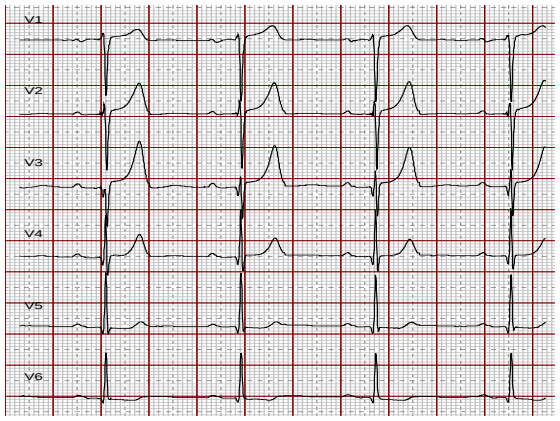
S., 1972





B., 1950





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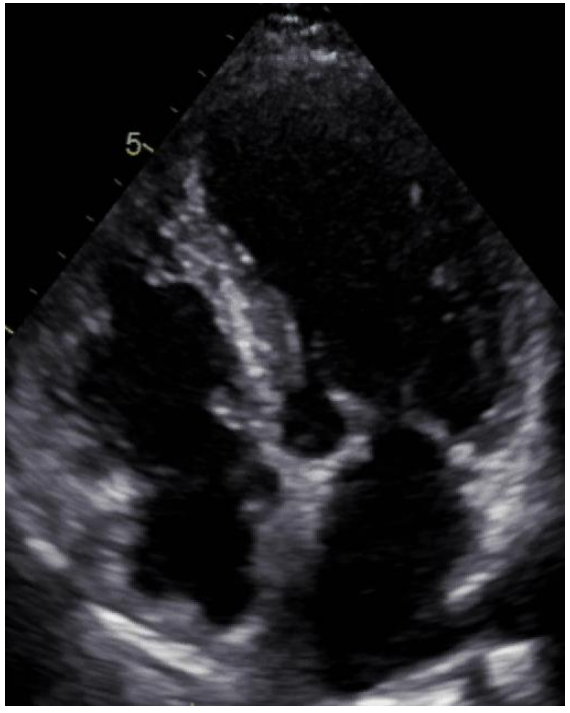
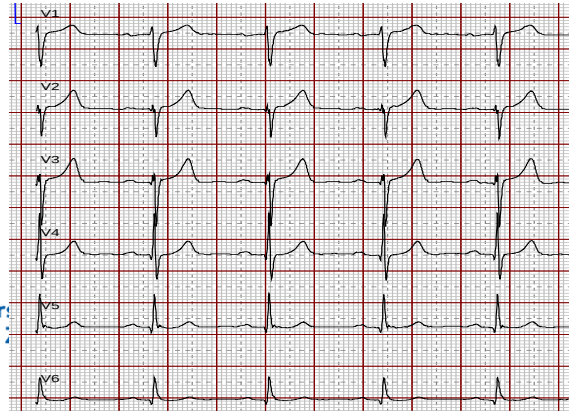
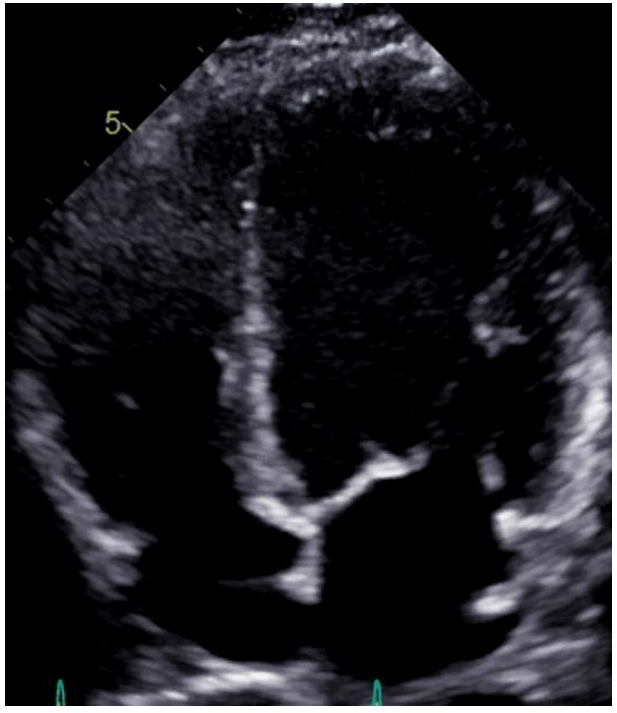
Case No 3, family members with positive genotype, negative phenotype

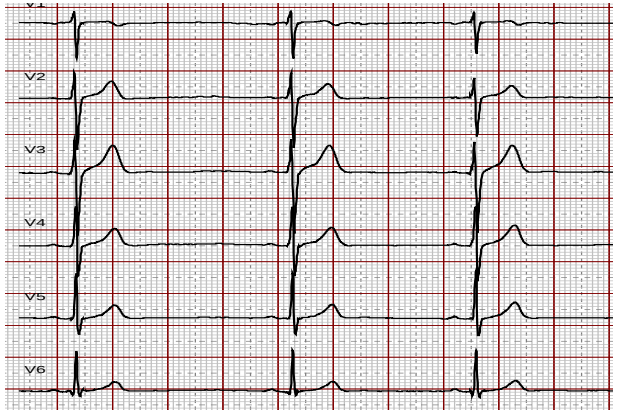
L., 1947



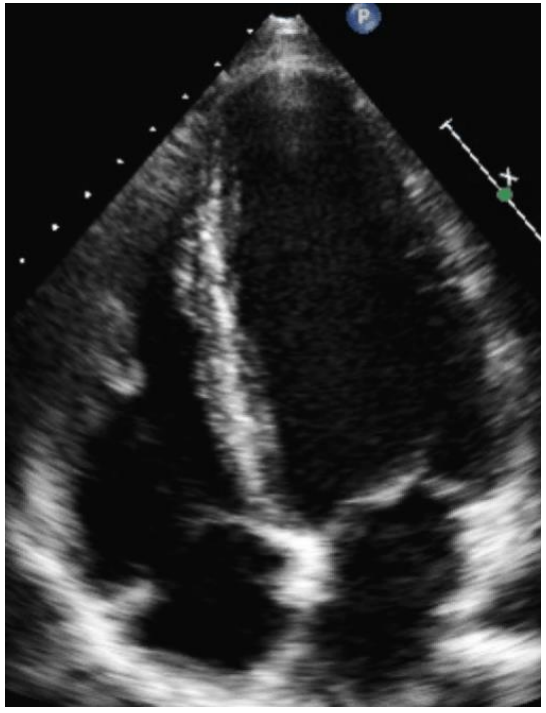


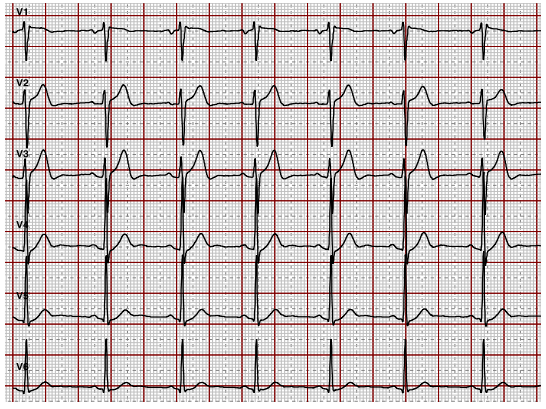
A., 1989





D., 1986





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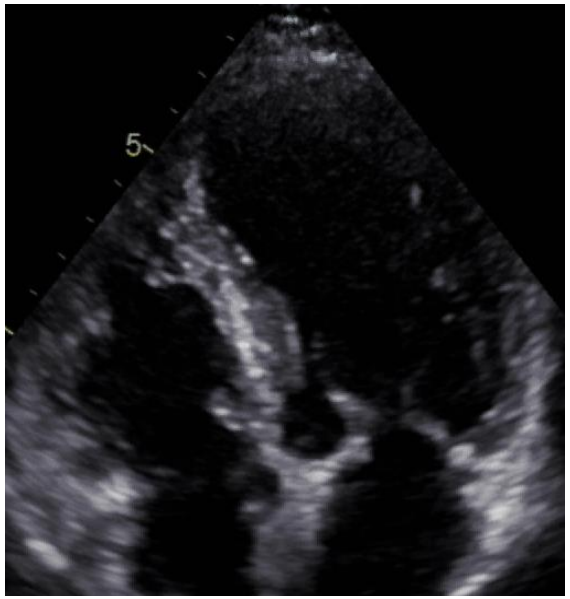
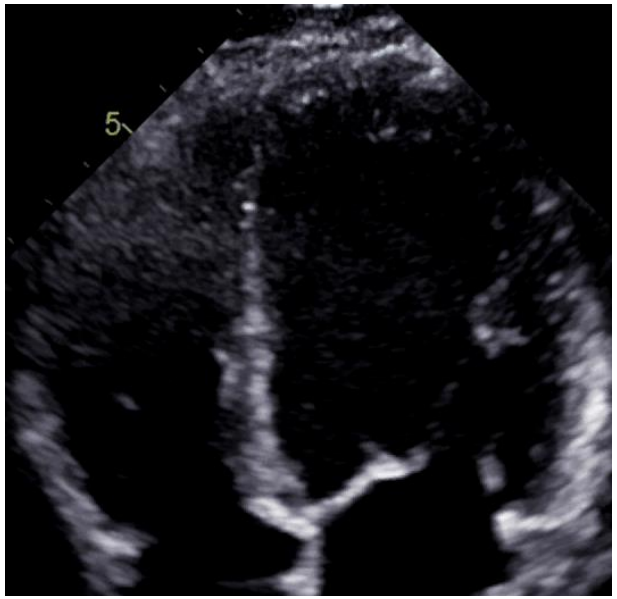
Case No 3, family members with positive genotype, negative phenotype

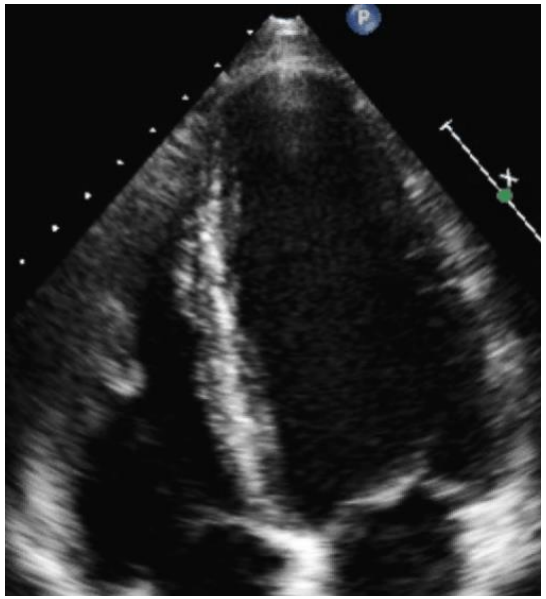
L., 1947



A., 1989



D., 1986



TAKE HOME MESSAGE # 4

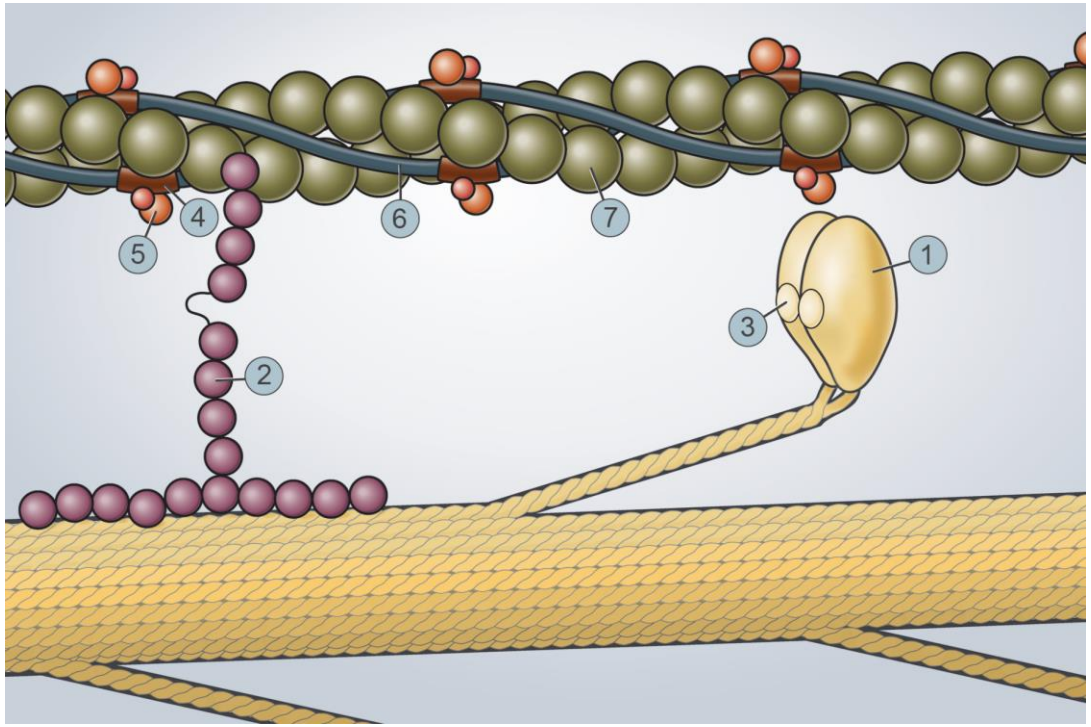
NO GENOTYPE PHENOTYPE CORRELATION

TAKE HOME MESSAGE # 5

FAMILY SCREENING MUST BE REPEATED

Genetics in hypertrophic cardiomyopathy

- autosomal dominant
- Prevalence 1:500 with HCM in general population



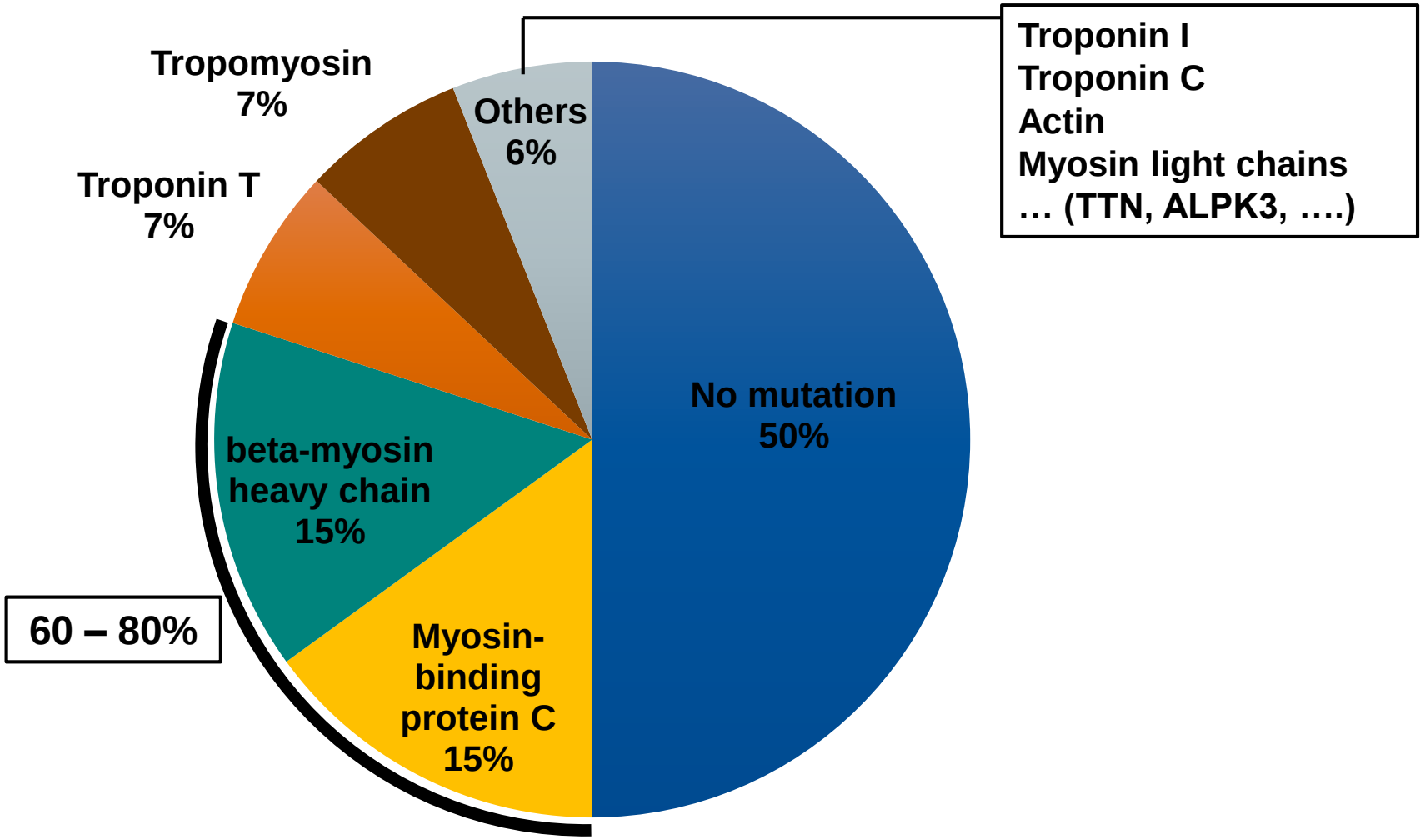
1 β-Myosin heavy chain
2 Myosin-binding protein-C
3 Myosin light chain 2 and 3
4 Troponin T
5 Troponin I
6 Tropomyosin
7 Actin

Phenocopies

- Fabry's disease
- PRKAG2 cardiomyopathy
- Danon's disease
- TTR amyloidosis

CURRENT PANELS INCLUDE >100 CMP GENES

Genetics in hypertrophic cardiomyopathy

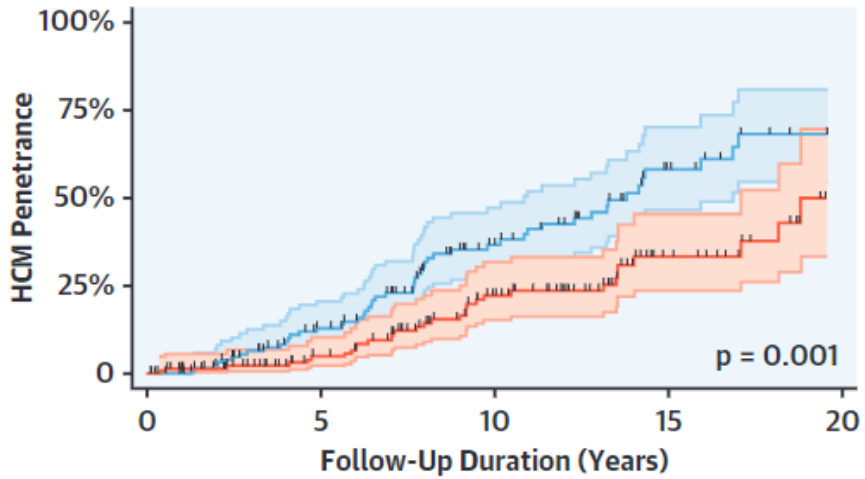


Genetics in hypertrophic cardiomyopathy, penetrance

CENTRAL ILLUSTRATION **Kaplan-Meier Estimates of Penetrance of Hypertrophic Cardiomyopathy in the Study Cohort by Sex**

285 adult and pediatric carriers of pathogenic/likely pathogenic sarcomere protein variants with no hypertrophic cardiomyopathy (HCM)

→ Penetrance of HCM at 15-year follow-up: 46% (95% CI: 38%-54%)



Number at risk

Male	141	91	45	16	5
Female	144	106	64	22	5

Risk factors for HCM

Male
HR: 2.91
(95% CI: 1.82-4.65)

Abnormal ECG
HR: 4.02
(95% CI: 2.51-6.44)

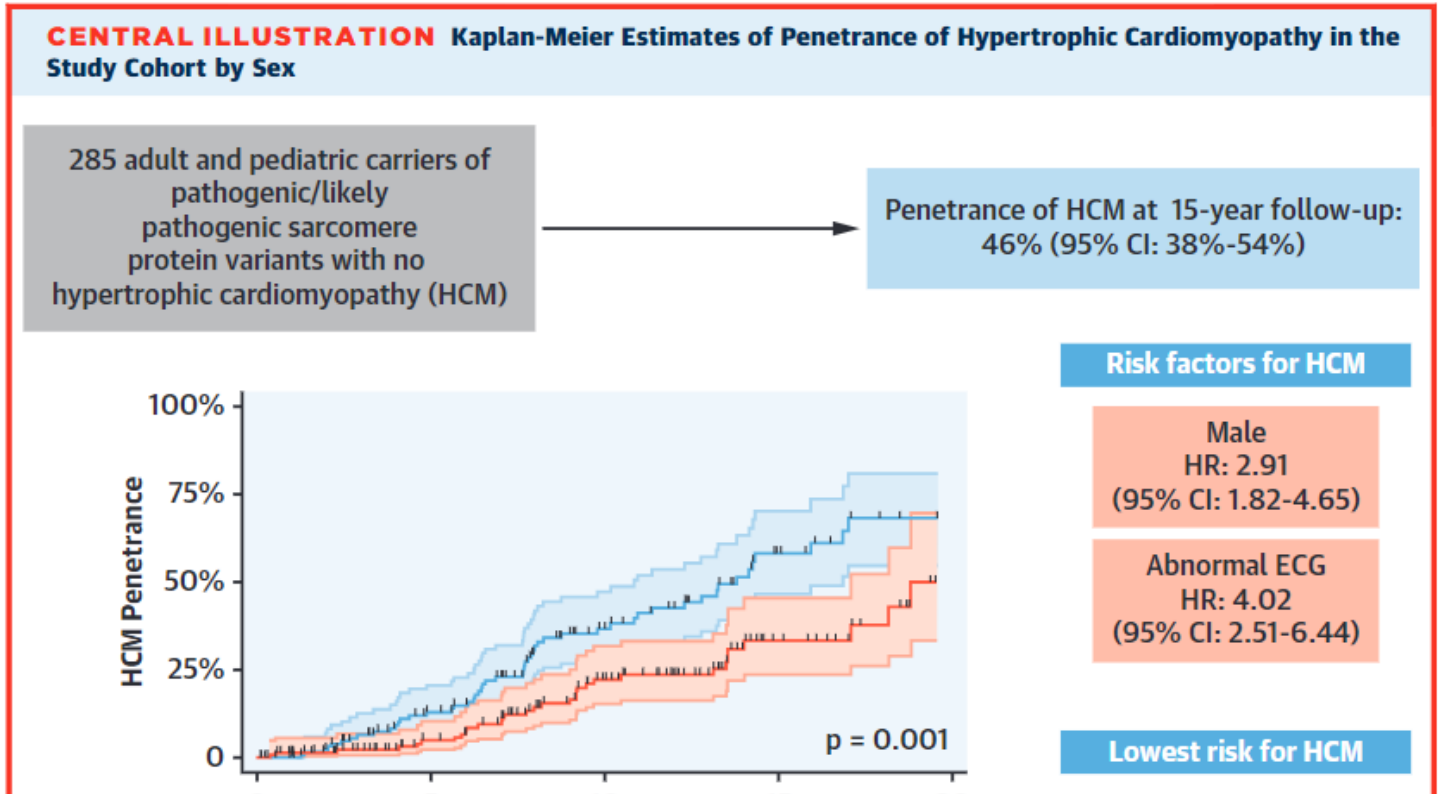
Lowest risk for HCM

TNNI3 variants
HR: 0.19
(95% CI: 0.07-0.55)

Lorenzini, M. et al. J Am Coll Cardiol. 2020;76(5):550-9.

Male sex and abnormal electrocardiogram are risk factors for penetrance of hypertrophic cardiomyopathy (HCM) in carriers of pathogenic/likely pathogenic variants in sarcomere genes, while *TNNI3* variants are protective.

Genetics in hypertrophic cardiomyopathy, penetrance



TAKE HOME MESSAGE # 6

NO GENETICS WITHOUT CARDIAC GENETICIST

Thank you

christiane.gruner@usz.ch

USZ Universitäts Spital Zürich