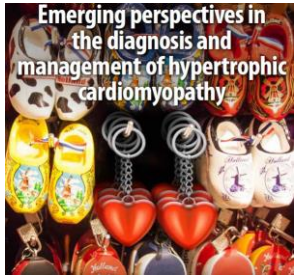
Diagnosing hypertrophic cardiomyopathy: What a cardiologist needs to know

Aleš Linhart, MD, PhD
- General University Hospital in Prague
- Charles University
Prague, Czech Republic

Emerging perspectives in the diagnosis and management of hypertrophic cardiomyopathy



PHYSICIANS' ACADEMY FOR
PACE-CME
CARDIOVASCULAR EDUCATION

Disclosures

- No disclosures for this session

Hypertrophic cardiomyopathy?

Presence of increased left ventricular (LV) wall thickness that is not solely explained by abnormal loading conditions.

In an adult ≥15 mm in one or more LV myocardial segments—by any imaging technique

- ~ **In relatives ≥13 mm**
- ~ **Genetic & nongenetic disorders 13–14 mm**

In children > 2 SD of the predicted mean **(z-score >2)**

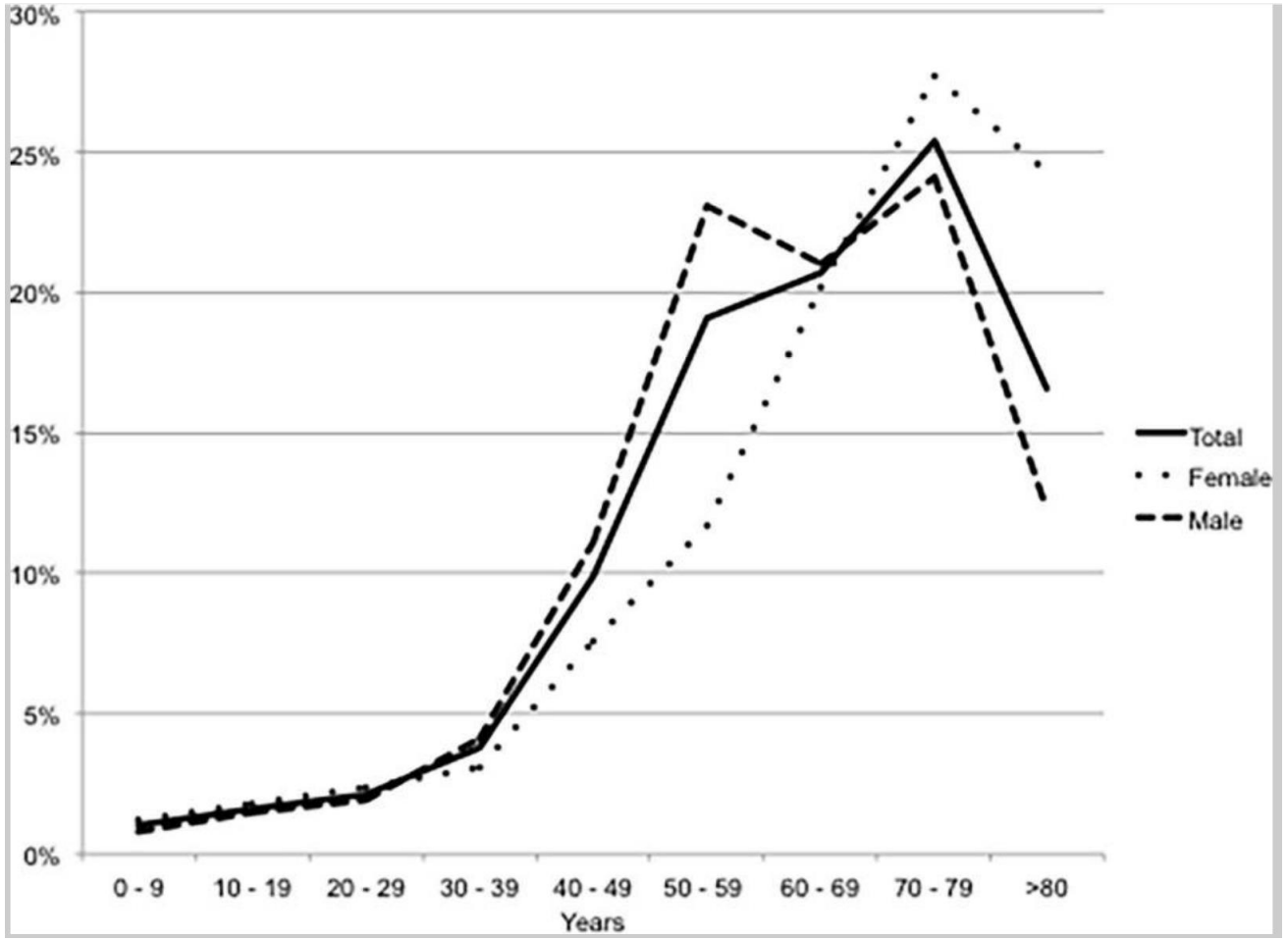
Elliott et al. Eur Heart J. 2014 Oct 14;35(39):2733-79.

Prevalence of diagnosed HCM in Germany (2015)[1]

- 4,000 out of 5,490,810 patients (0.07%; 1:1,372)
- average age 63±17 years (median 66 years),
- 2,586 (65%) were male.

Prevalence lower as compared to original echo-based data from Coronary Artery Risk Development in (Young) Adults (CARDIA) Study[2]

- **4111 men and women 23 to 35 years of age selected from the general population**
- **7 (0.17%) fulfilled the criteria for HCM**
- **Prevalence in men and women was 0.26:0.09%;**
- **Prevalence in blacks and whites 0.24:0.10%**



1. Husser D et al. PLoS One. 2018; 13(5): e0196612.
2. Maron BJ et al. Circulation. 1995;92:785–789

European Heart Journal Advance Access published December 4, 2012

European Heart Journal
doi:10.1093/eurheartj/ehs397

SPECIAL ARTICLE

Diagnostic work-up in cardiomyopathies: bridging the gap between clinical phenotypes and final diagnosis. A position statement from the ESC Working Group on Myocardial and Pericardial Diseases

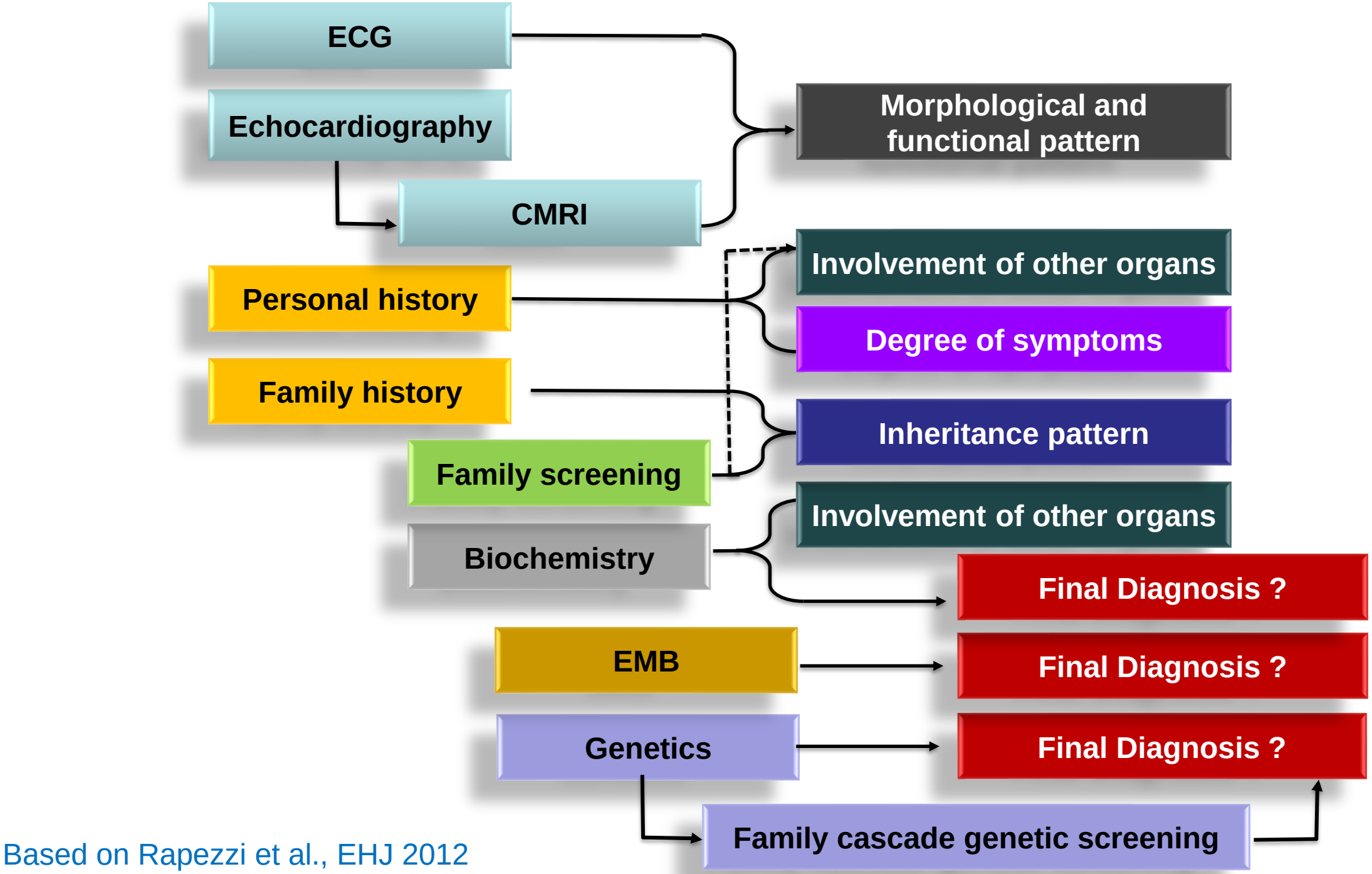
Claudio Rapezzi, Eloisa Arbustini, Alida L. P. Caforio, Philippe Charron, Juan Gimeno-Blanes, Tiina Heliö, Ales Linhart, Jens Mogensen, Yigal Pinto, Arsen Ristic, Hubert Seggewiss, Gianfranco Sinagra, Luigi Tavazzi, and Perry M. Elliott*

The Heart Hospital, 16–18 Westmoreland Street, London W1G 8PH, UK

Received 6 May 2012; revised 3 September 2012; accepted 20 September 2012

In 2008, The ESC Working Group on Myocardial and Pericardial Diseases proposed an updated classification of cardiomyopathies based on morphological and functional phenotypes and subcategories of familial/genetic and non-familial/non-genetic disease. In this position statement, we propose a framework for the clinical approach to diagnosis in cardiomyopathies based on the recognition of diagnostic 'red flags' that can be used to guide rational selection of specialized tests including genetic analysis. The basic premise is that the adoption of a cardiomyopathy-specific mindset which combines conventional cardiological assessment with non-cardiac and molecular parameters increases diagnostic accuracy and thus improves advice and treatment for patients and families.

Keywords Cardiomyopathy • Diagnosis • Phenotype • Genotype



Based on Rapezzi et al., EHJ 2012

Patient´s trajectory in cardiology practice

Symptoms

- Heart failure
- Arrhythmias
- Syncope
- Sudden death

Asymptomatic

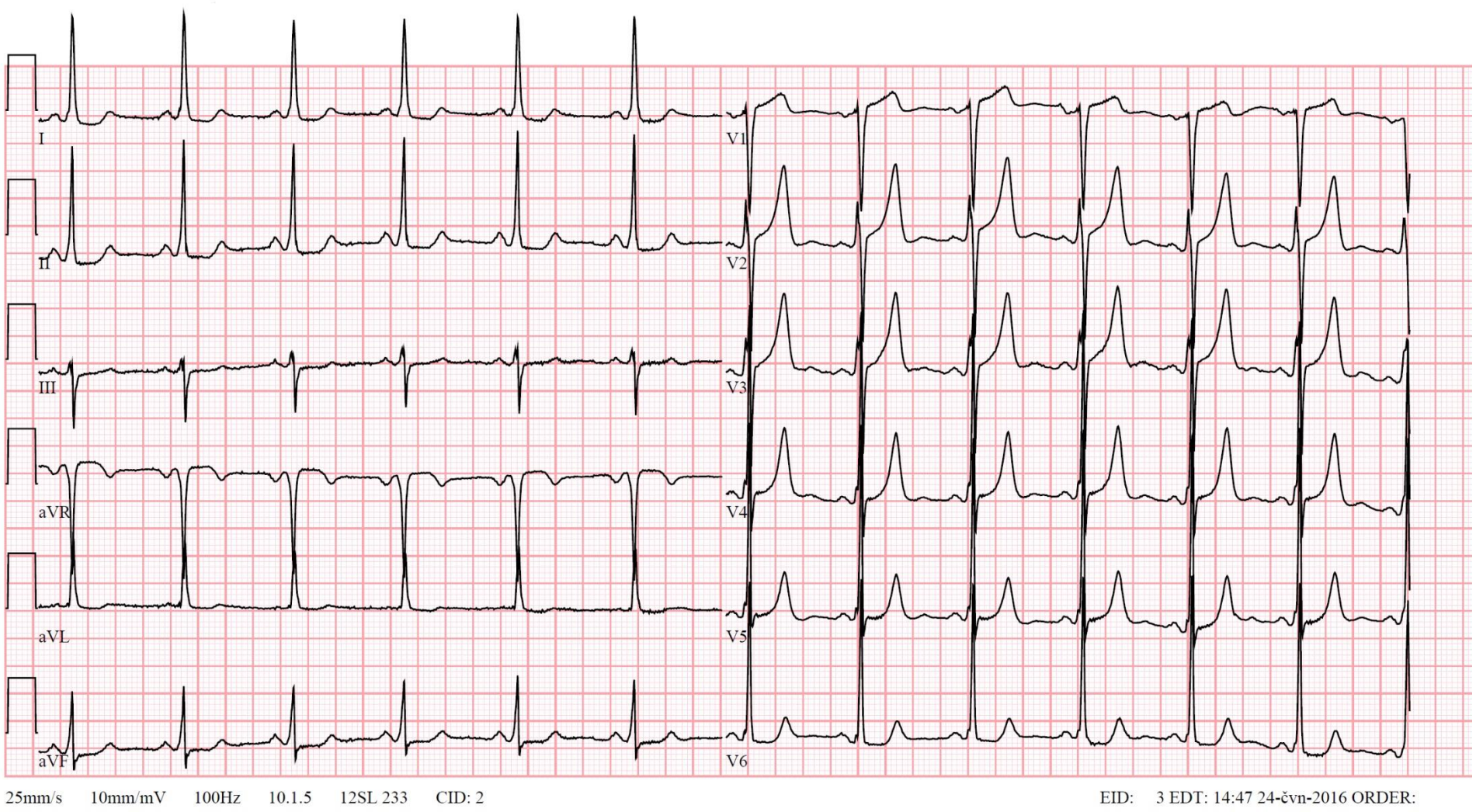
- Screening (ECG, ECHO)

HCM diagnosis in a relative

Author´s own opinion

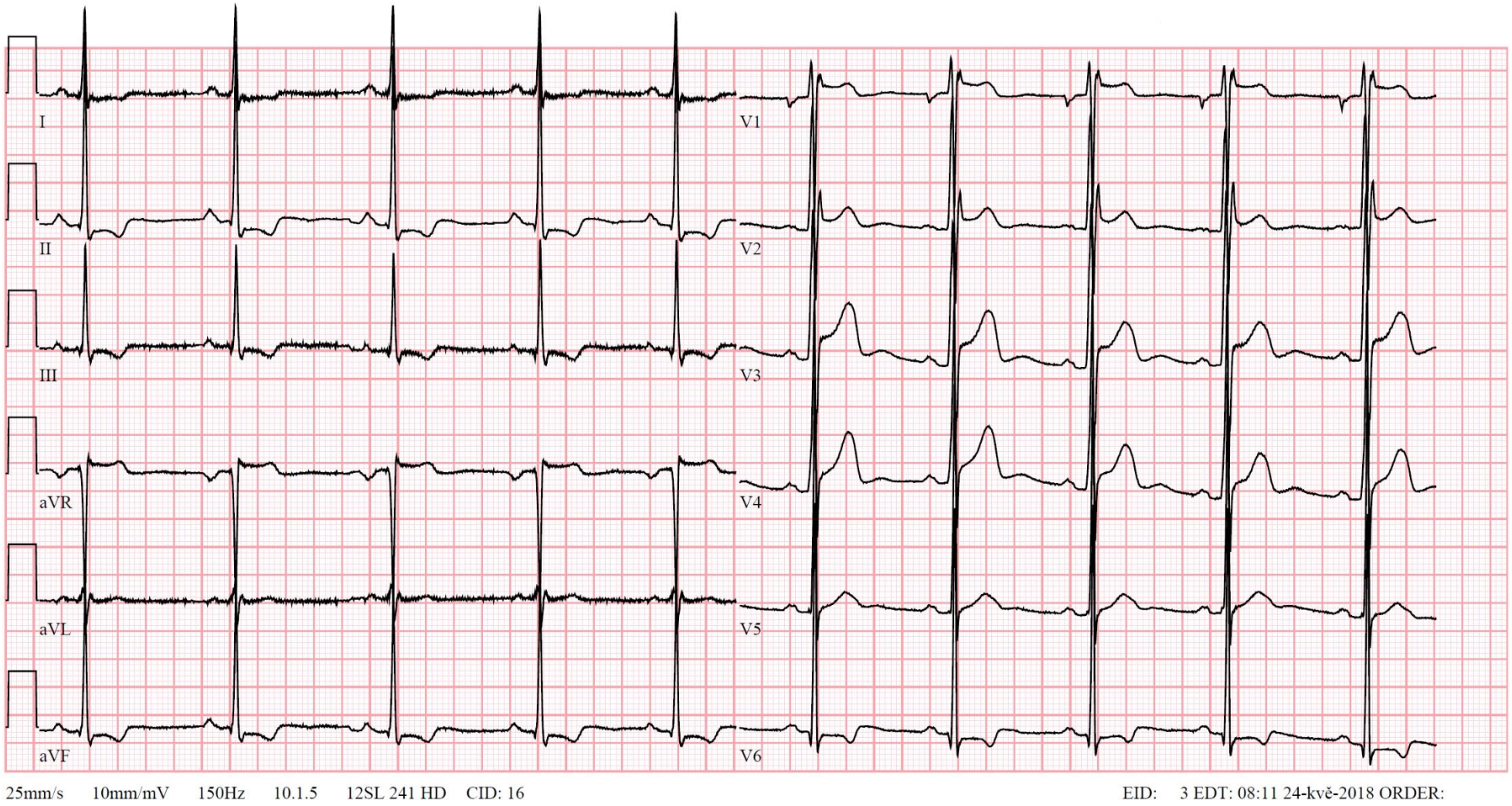
STEP 1: HYPETROPHY

HCM – genetic testing negative



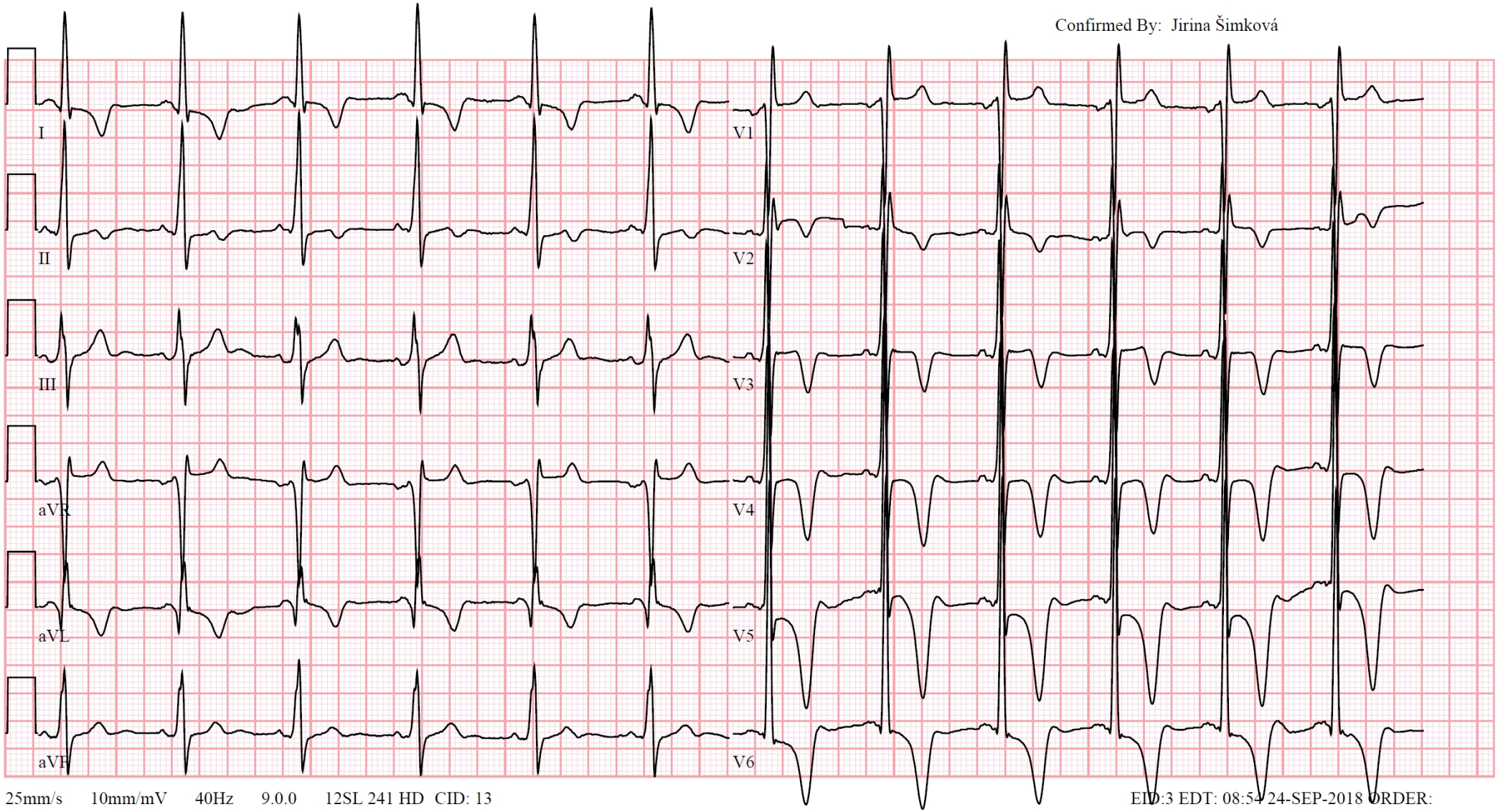
Images: General University Hospital, Prague

Sarcomeric HCM + genetic variant associated with Brugada syndrome

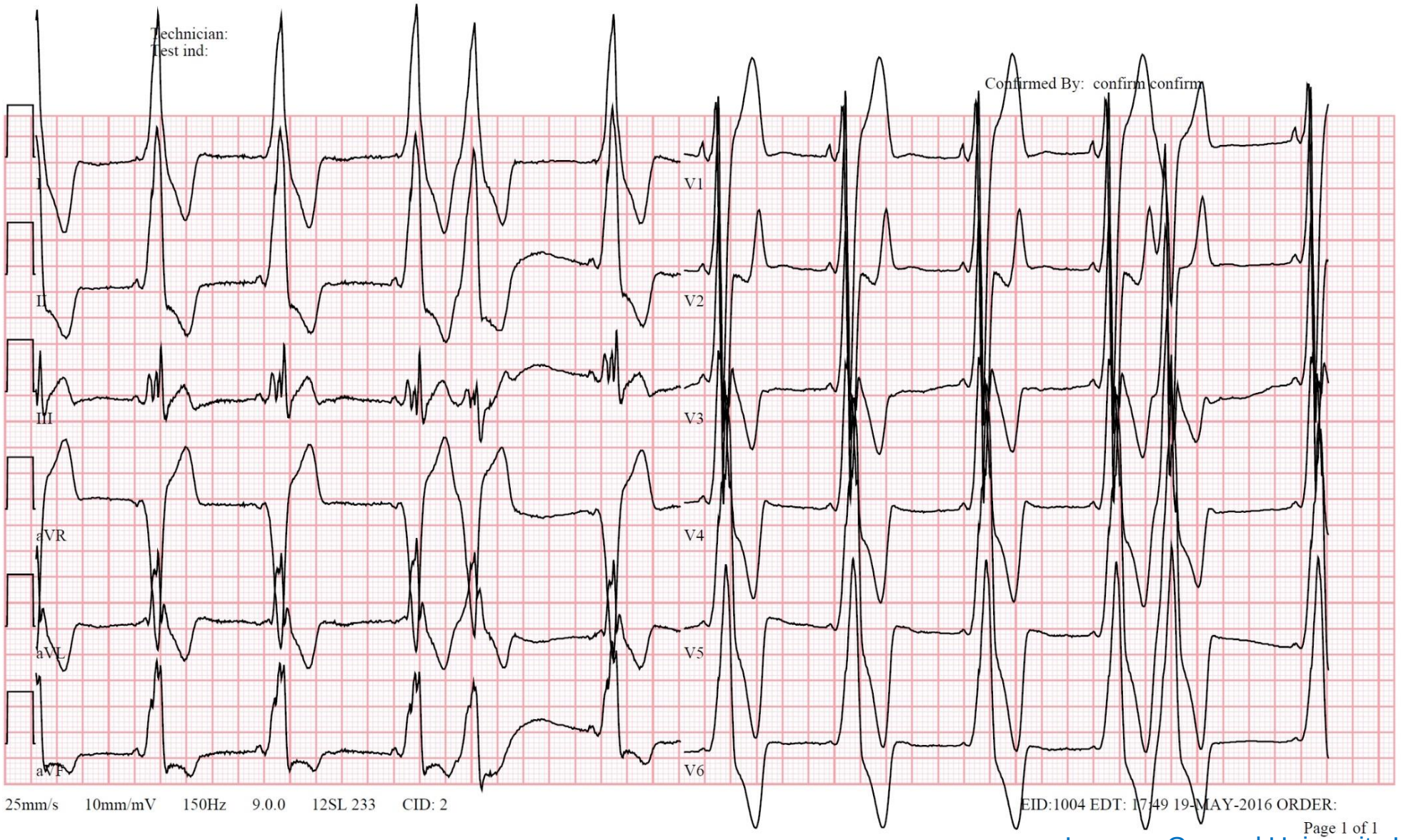


Images: General University Hospital, Prague

Anderson Fabry disease



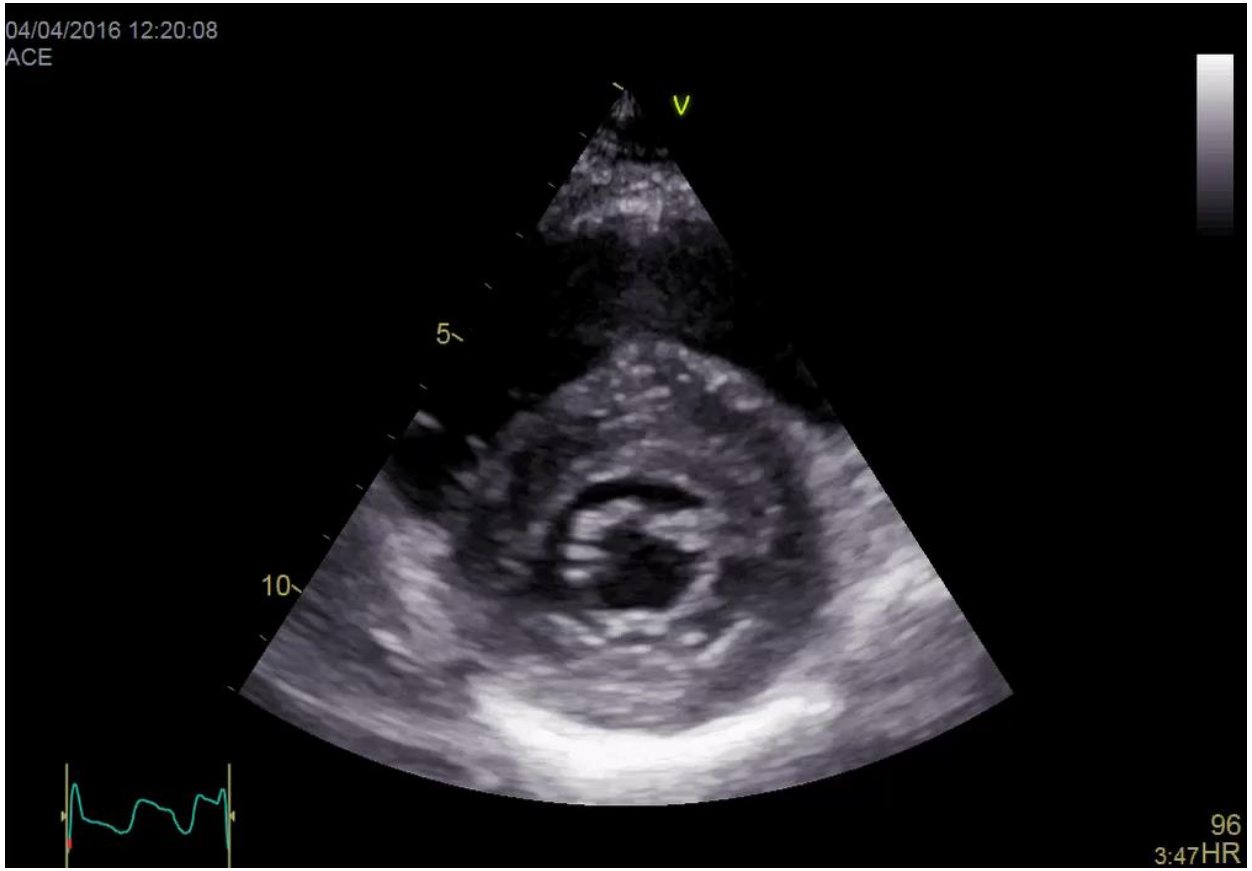
Danon disease



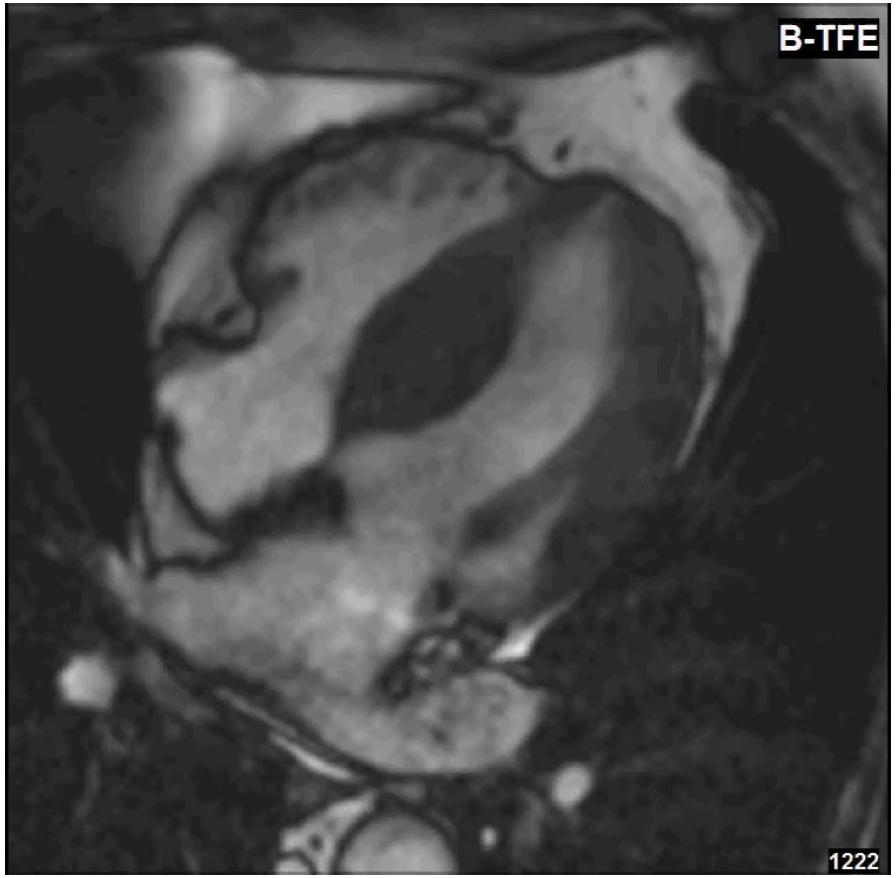
Images: General University Hospital, Prague

Based on Guidelines, any thickening over 15 mm without other conditions is sufficient

Echocardiography

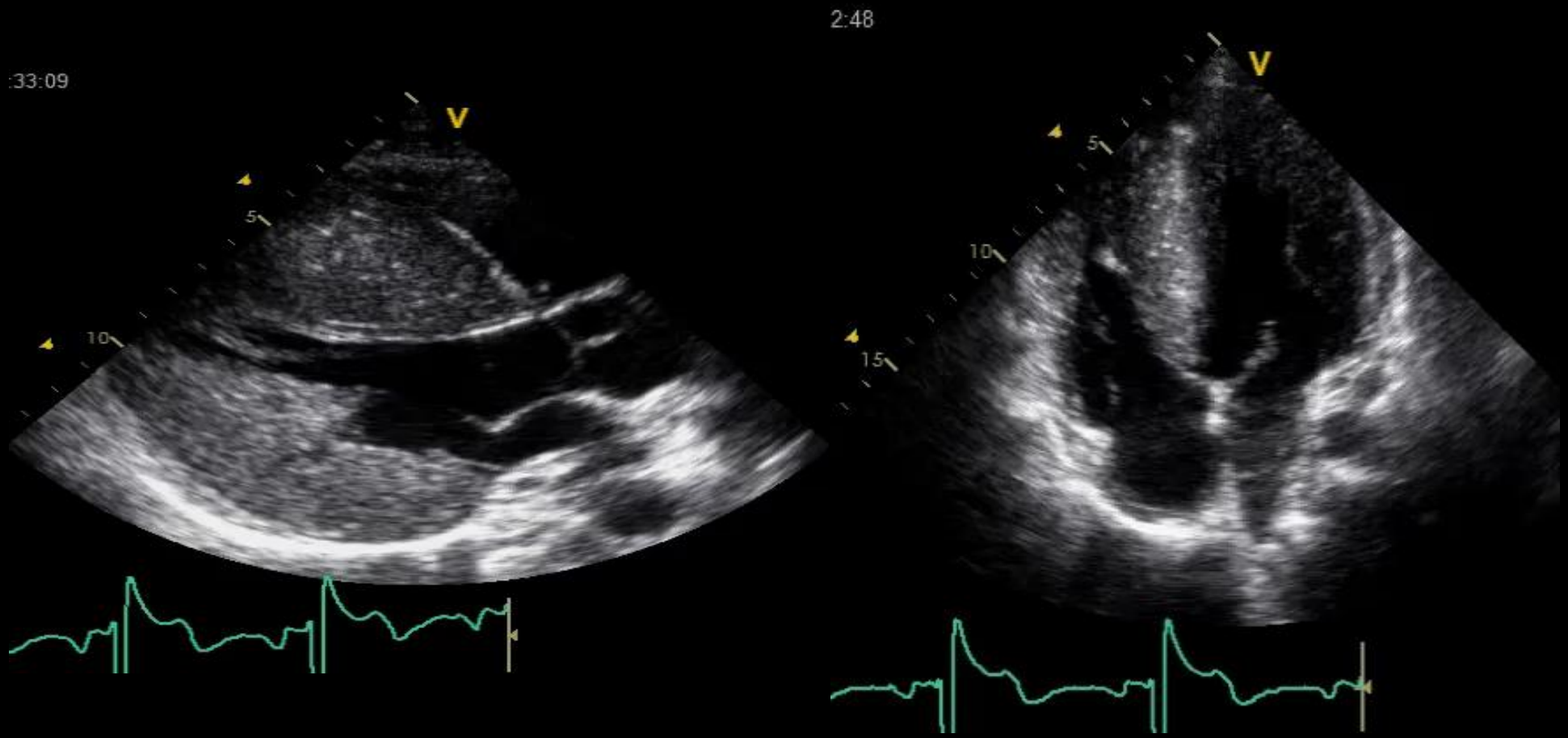


Cardiac Magnetic Resonance



Images: General University Hospital, Prague

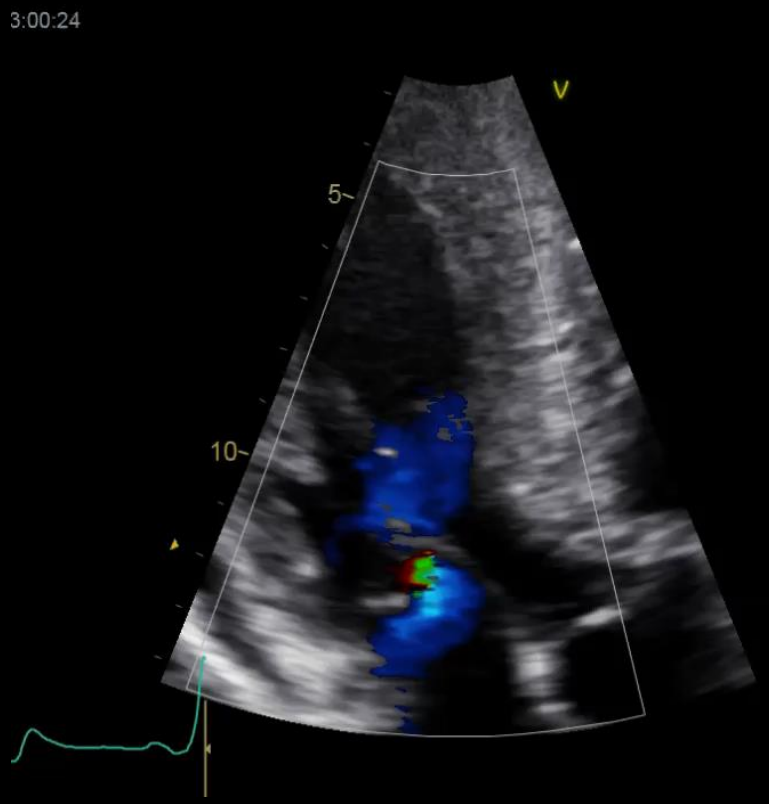
Severe homogenous hypertrophy

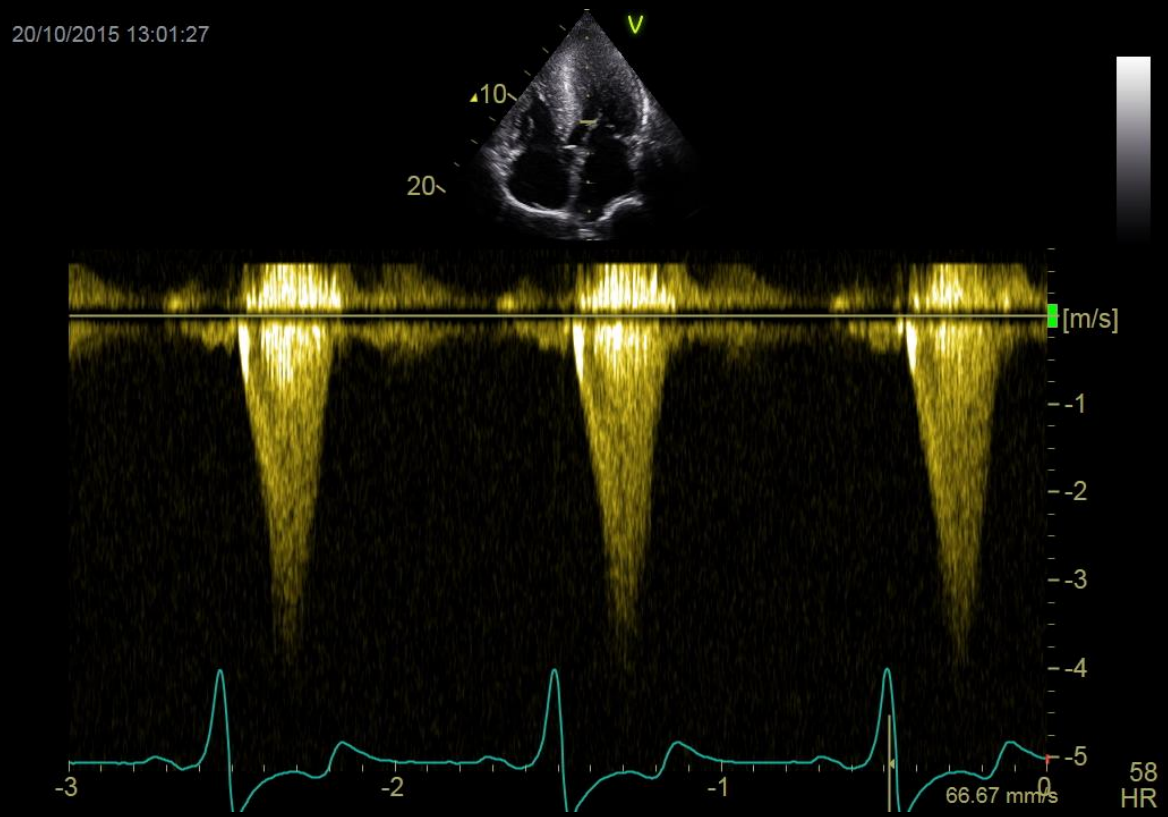


Imaging: General University Hospital, Prague, Czech Republic

STEP 2: „OBSTRUCTIVE“ CARDIOMYOPATHY

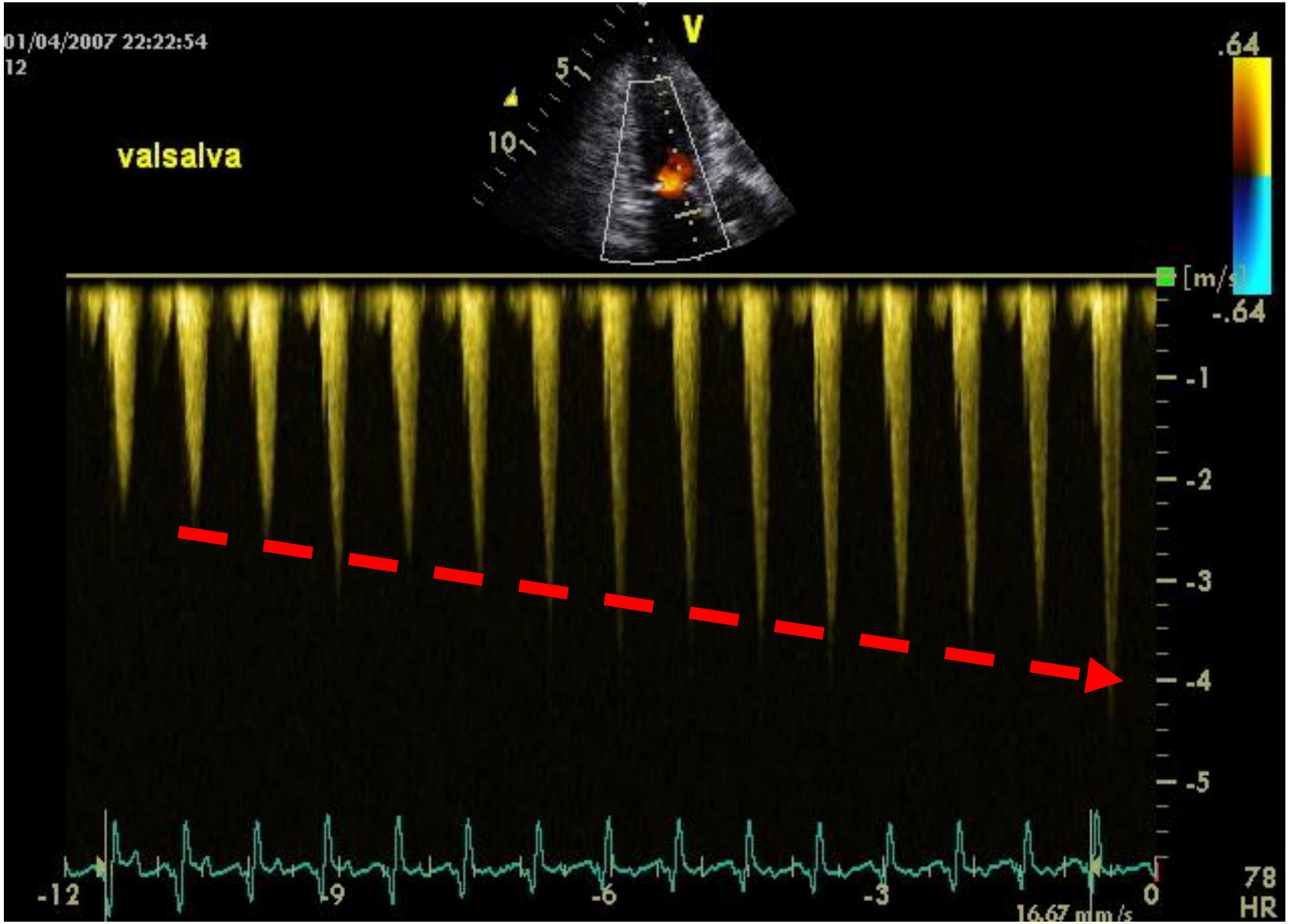
Classical Cause of LVOTO





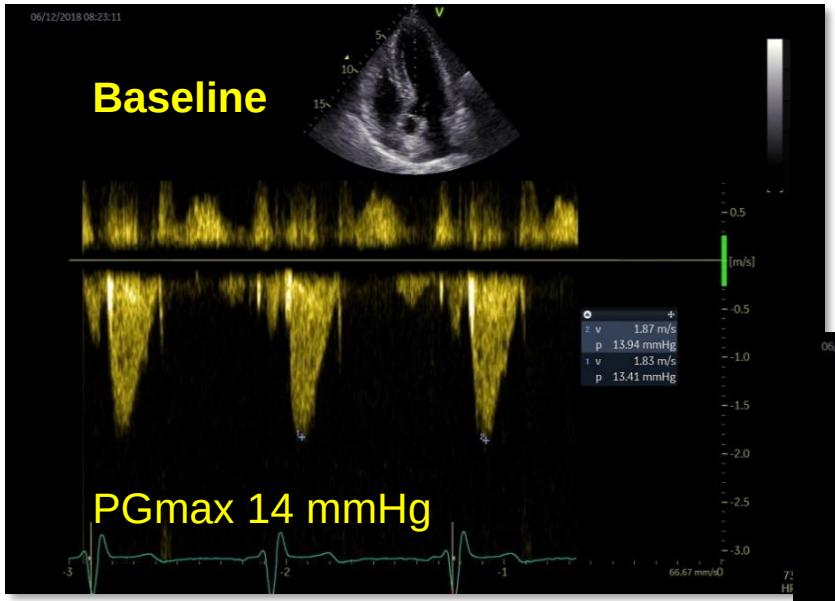
Imaging: General University Hospital, Prague, Czech Republic

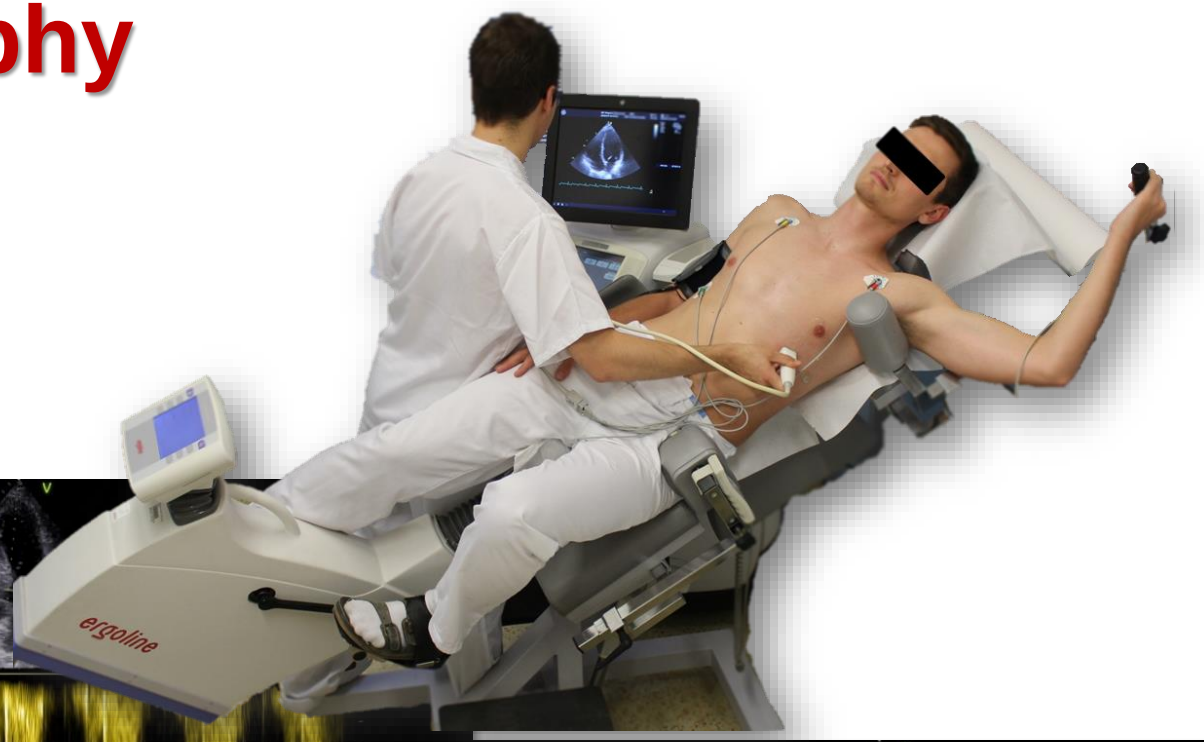
LVOTO Gradient Increasing During the Valsalva Maneuver

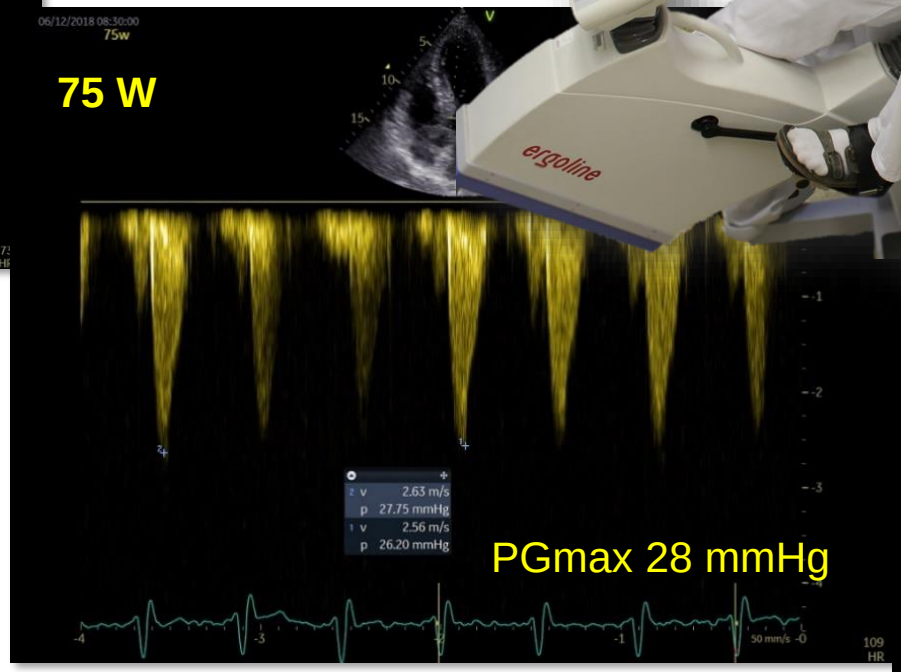


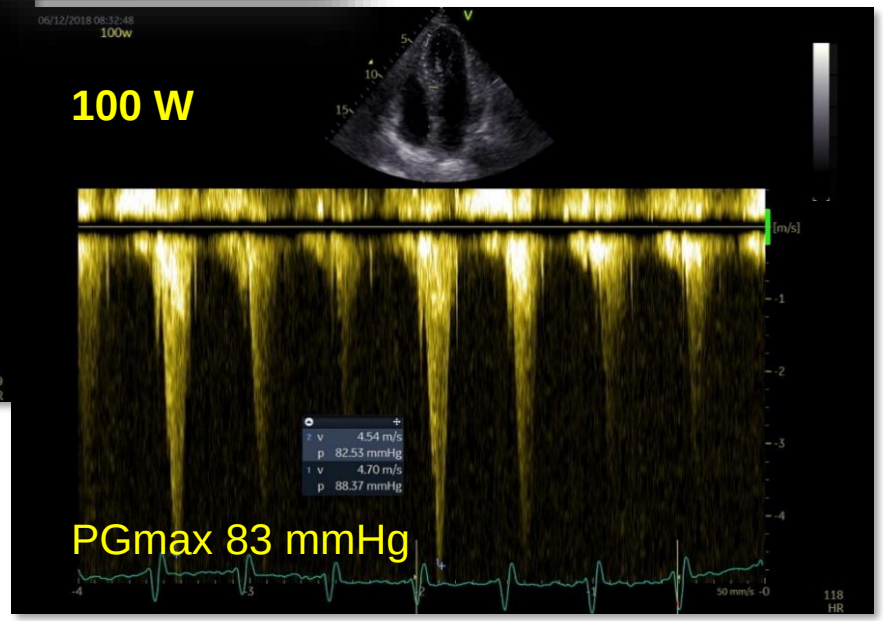
Imaging: General University Hospital, Prague, Czech Republic

Exercise echocardiography







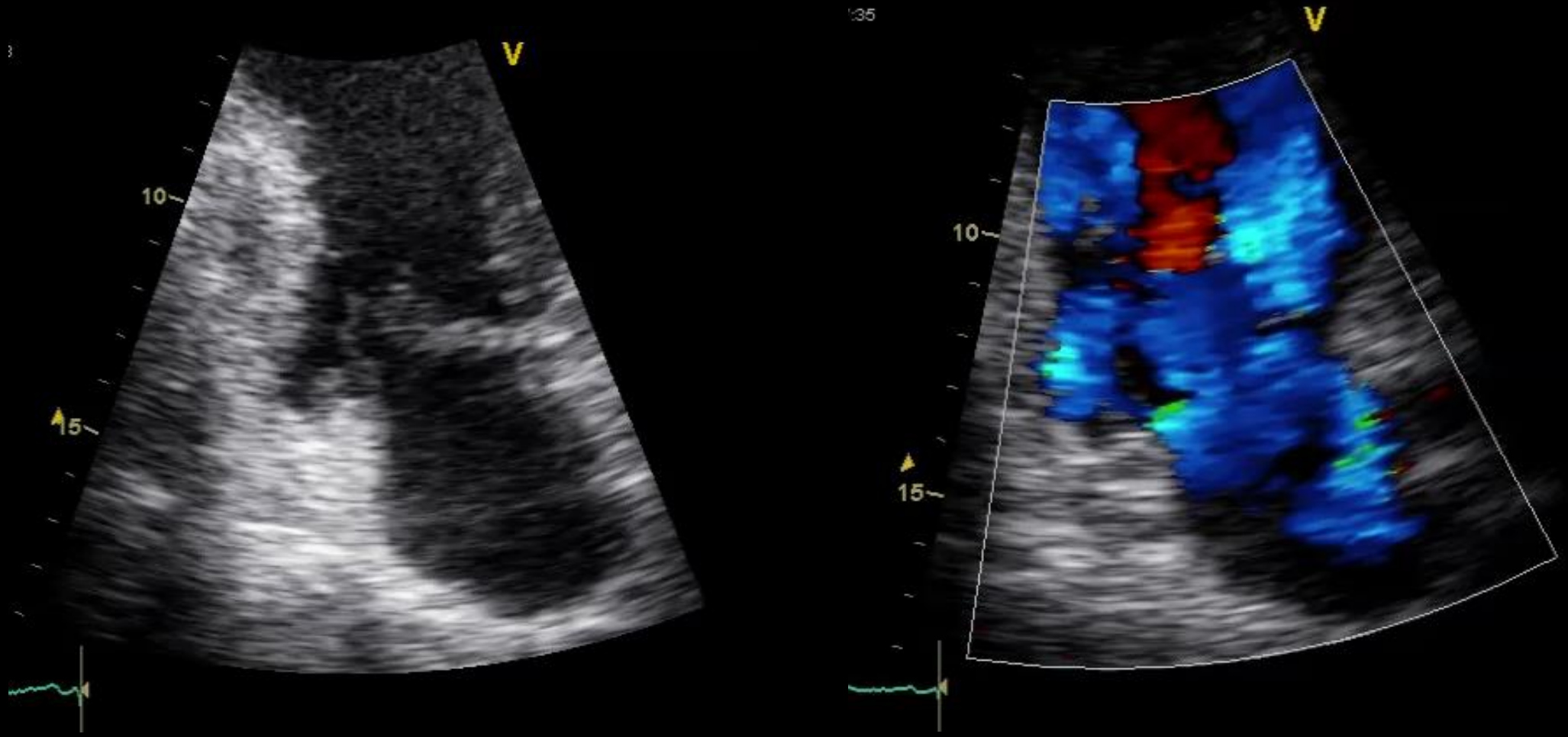


37% - obstruction at rest
33% - provoked obstruction

1. Maron MS, et al. *Circulation.* 2006;114:2232-2239.2. Maron MS, et al. *J Am Coll Cardiol.* 2016;67:1399-1409.
3. Rowin EJ, et al. *JACC Cardiovasc Imaging.* 2017;10:1374-1386. 4. Elliott PM, et al. *Eur Heart J.* 2006;27:1933-41.

Imaging: General University Hospital, Prague, Czech Republic

Mitral regurgitation in HCM

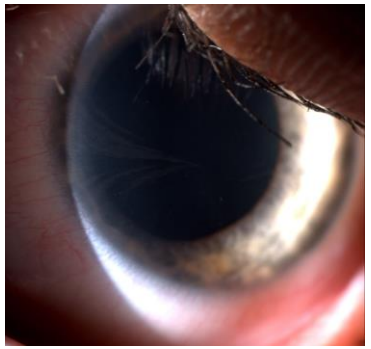


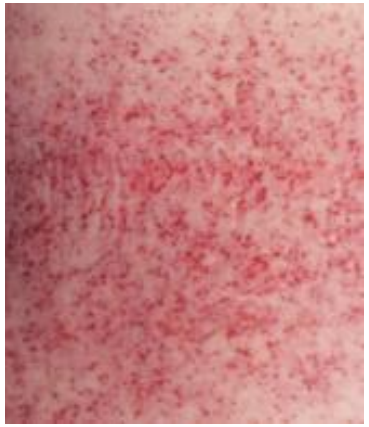
Imaging: General University Hospital, Prague, CZ

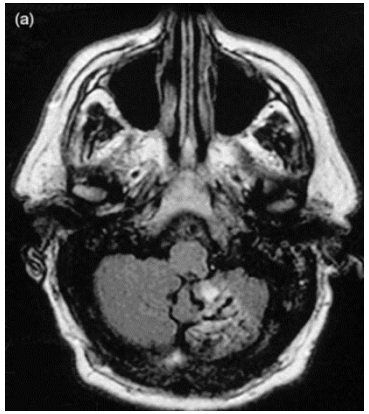
STEP 3: DIFFERENTIAL DIAGNOSIS

Associated extracardiac involvement

- Mental retardation
  - Mitochondrial
  - Danon
  - Noonan sy
- Sensorineural deafness
  - Mitochondrial
  - Friedreich
  - Fabry
- Visual impairment
  - Fabry
  - Danon
- Gait disturbances
  - Friedreich´s ataxia
- Neuropathy / neuropathic pain
  - Amyloidosis
  - Fabry
- Muscle weakness
  - Mitochondrial
  - Glycogenosis
  - Friedreich
- Cutaneous changes
  - Fabry
  - Hemochromatosis
- Renal involvement
  - Fabry







Rapezzi et al. EJH 2012

Cases and images: General University Hospital Prague, CZ

Laboratory findings

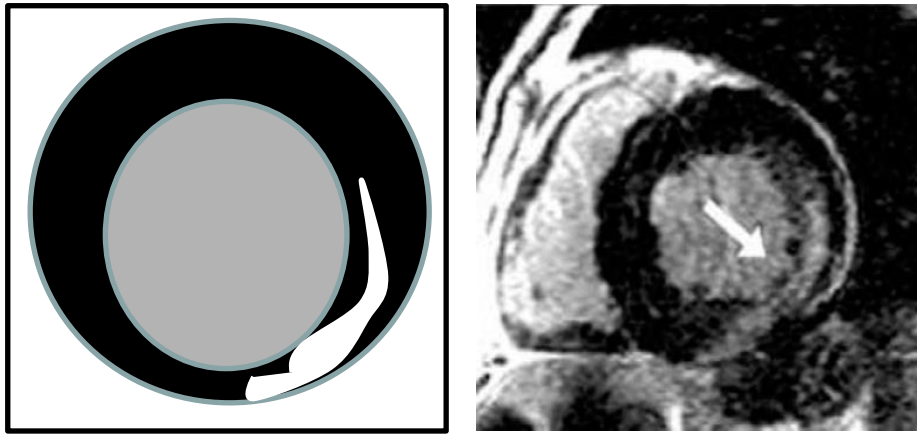
- Elevated CPK
- Lactate
- NT-proBNP
- hs-cTn
- LFT
- Myoglobinuria
- Serum creatinine
- Proteinuria

- Enzymatic activity
  - Fabry, Pompe
- Specific markers
  - Lyso-Gb3 - Fabry
- Serum/urine immunofixation
- Serum free light chain (sFLC) ratio

Rapezzi et al. EJH 2012

LGE distribution in Fabry and other cardiomyopathies

Fabry

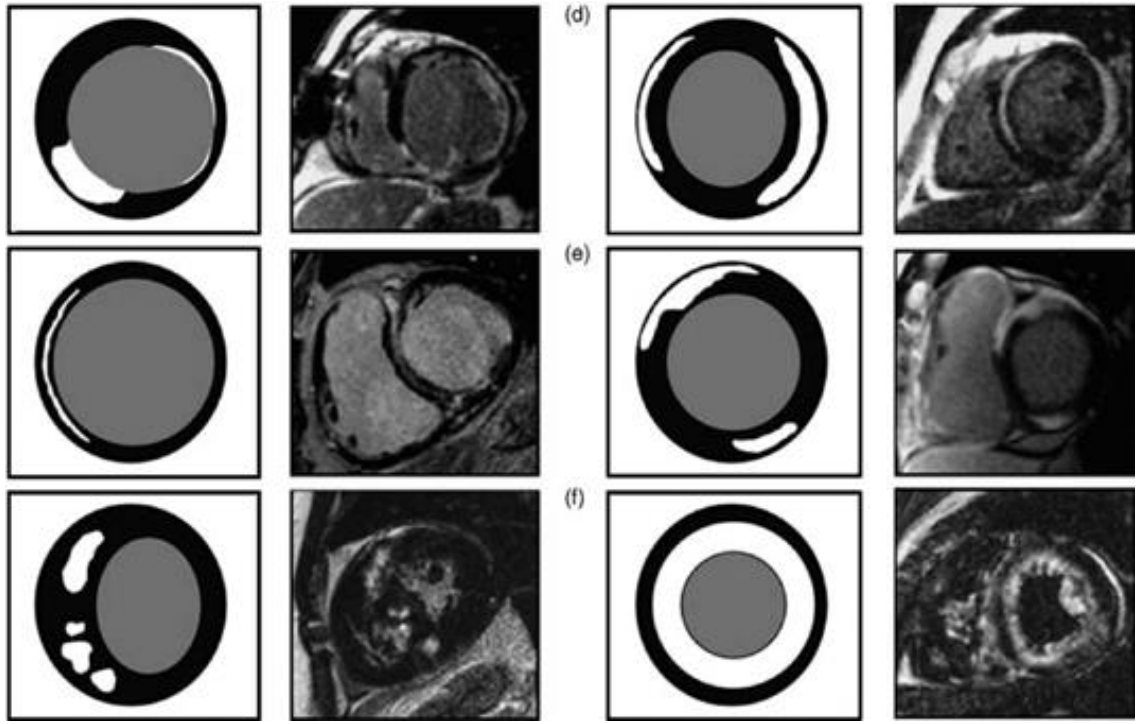


Moon al., Eur Heart J (2003)

CHD

DCM

HCM



Myocarditis

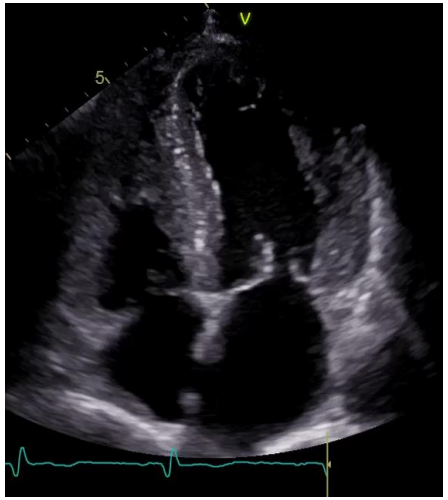
Sarcoidosis

Amyloidosis

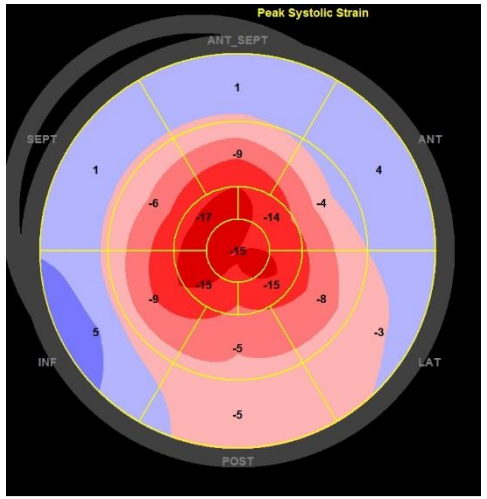
White JA, Patel MR. Cardiol Clin. (2007)

Amyloidosis

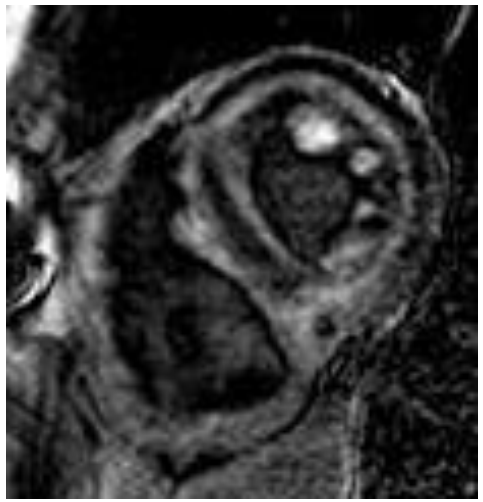
- Echocardiography
  - Pattern & Degree of LVH
  - Apical sparing
  - Additional features
    - Valvular involvement
    - Pericardial effusion
    - IAS infiltration
- MRI
  - Pattern of hypertrophy
  - LGE distribution
  - T1 mapping
- Bone scintigraphy
  - Bisphosphonate accumulation



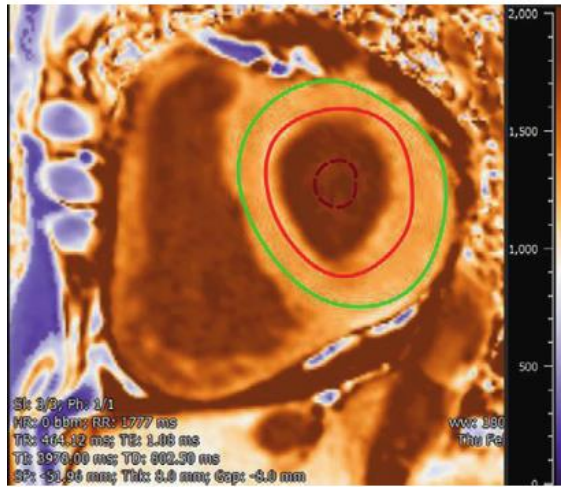
2D echo
- LVH RVH
- IAS thickening
- Valvular thickening



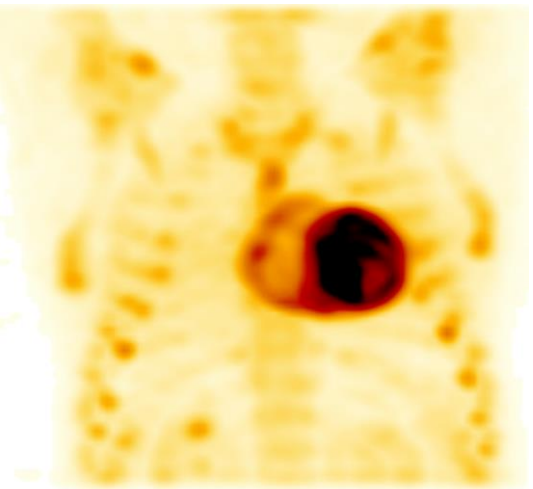
Speckle tracking
- Apical sparing



MRI - LGE
- Subendocardial enhancement



MRI – T1 mapping
- Long T1



^{99m}Tc -DPD scintigraphy
- Accumulation – Perugini score grade 3

Maceira A. et al., Circulation 2005;111: 186
Karamitsos et al. JACC: Cardiovascular Imaging, 2013;6:498-500
Rapezzi et al. JACC Cardiovasc Imaging. 2011 Jun;4(6):659-70

Imaging: General University Hospital Prague, CZ

Clinical suspicion of cardiac amyloidosis (Echo, ECG, CMRI)

Serum / urine immunofixation

Serum free light chain (sFLC) ratio

DPD(PYP) scan

M-spike on immunofixation

Serum free light chain (sFLC) ratio
- High (>1.65) = kappa
- Low (<0,26) = Lambda

Grade 0/1 DPD(PYP) uptake

No M-spike on immunofixation

Normal sFLC ratio

Grade 2-3 DPD(PYP) uptake

AL

Fat needle aspiration biopsy

Endomyocardial biopsy with LC/MS for typing

ATTR

Bone marrow biopsy

Genetic testing

Donnelly and Hanna Clevelend Clinic J Med 2017;84, suppl. 3: 12-18

ESC European Society of Cardiology

European Journal of Heart Failure (2021) **23**, 854–871
doi:10.1002/ejhf.2190

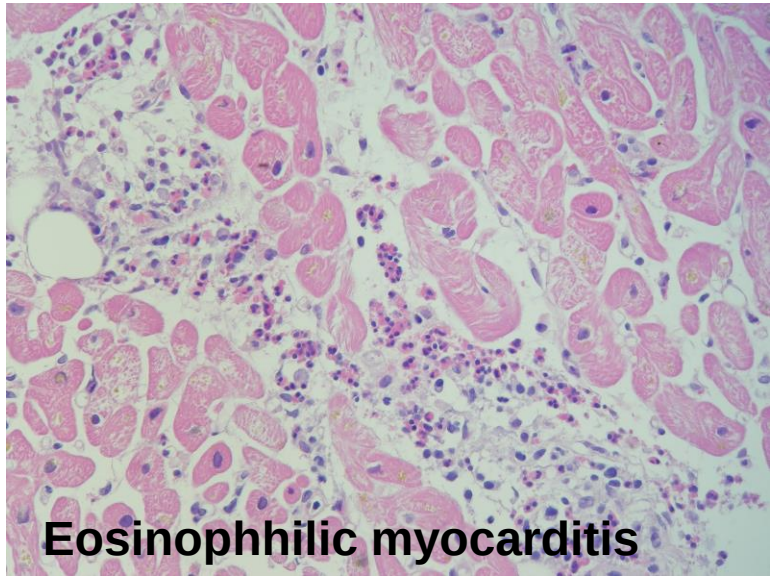
POSITION PAPER

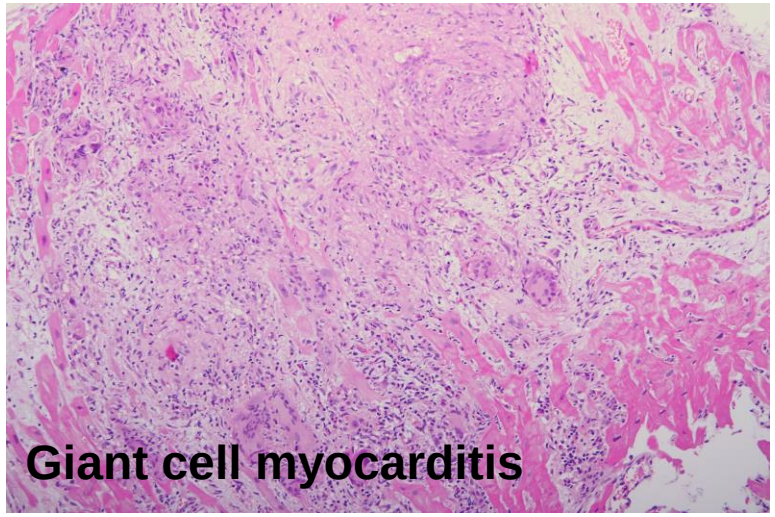
Heart Failure Association of the ESC, Heart Failure Society of America and Japanese Heart Failure Society Position statement on endomyocardial biopsy

Petar M. Seferović[1]*, Hiroyuki Tsutsui[2], Dennis M. McNamara[3], Arsen D. Ristić[4,5], Cristina Basso[6], Biykem Bozkurt[7], Leslie T. Cooper Jr[8], Gerasimos Filippatos[9], Tomomi Ide[2], Takayuki Inomata[10], Karin Klingel[11], Aleš Linhart[12], Alexander R. Lyon[13], Mandeep R. Mehra[14], Marija Polovina[4,5], Ivan Milinković[4,5], Kazufumi Nakamura[15], Stefan D. Anker[16], Ivana Veljić[4], Tomohito Ohtani[17], Takahiro Okumura[18], Thomas Thum[19,20], Carsten Tschöpe[21], Giuseppe Rosano[22], Andrew J.S. Coats[23,24], and Randall C. Starling[25]

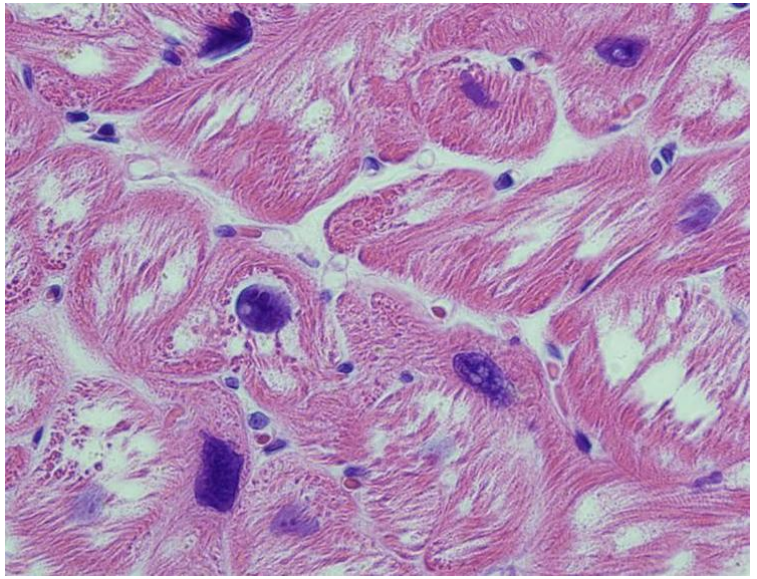
Endomyocardial biopsy

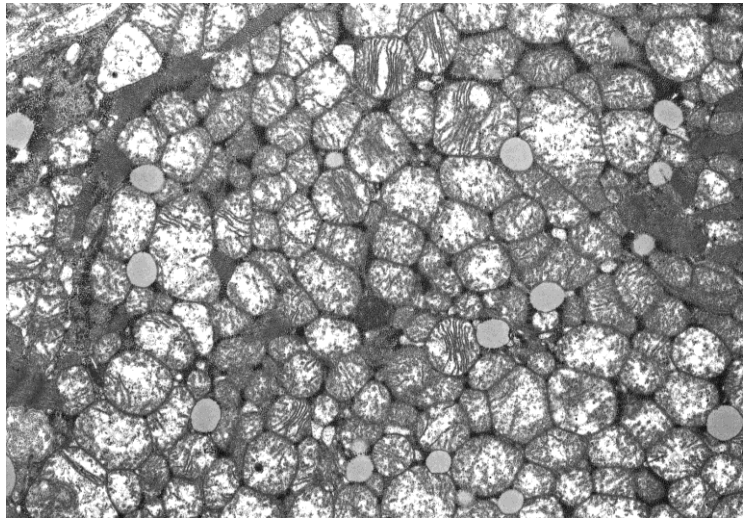
Myocarditis





Mitochondrial cardiomyopathy



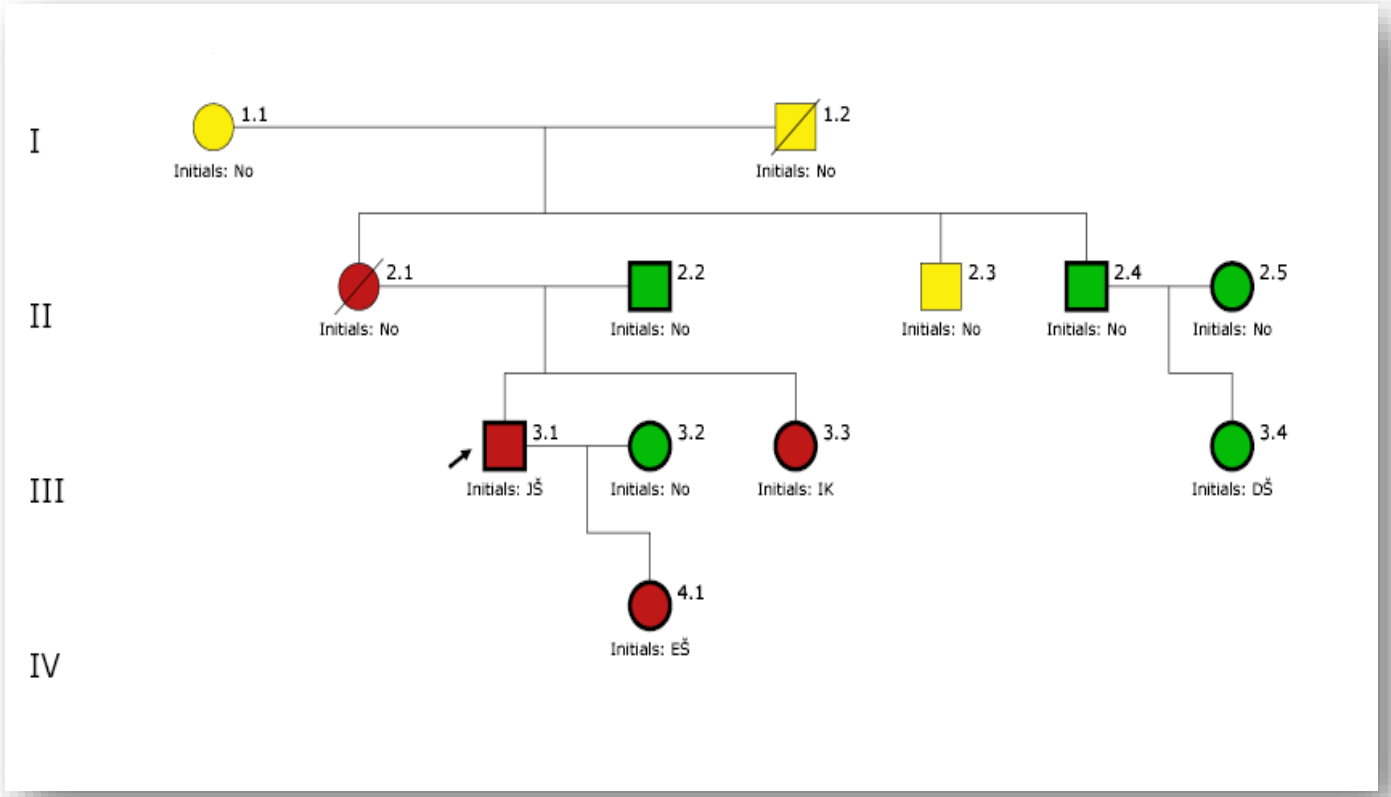


Source: General University Hospital, Prague, CZ

STEP 4: GENETIC TESTING

Inheritance pattern

- Autosomal dominant
  - Sarcomeric HCMs
  - Hereditary TTR amyloidosis
- Autosomal recessive
  - Pompe
  - Friedreich ataxia
- X-linked
  - Fabry
  - Danon
- Matrilinear
  - Mitochondrial DNA mutations



Imaging: General University Hospital Prague, CZ

Rapezzi et al. EJH 2012

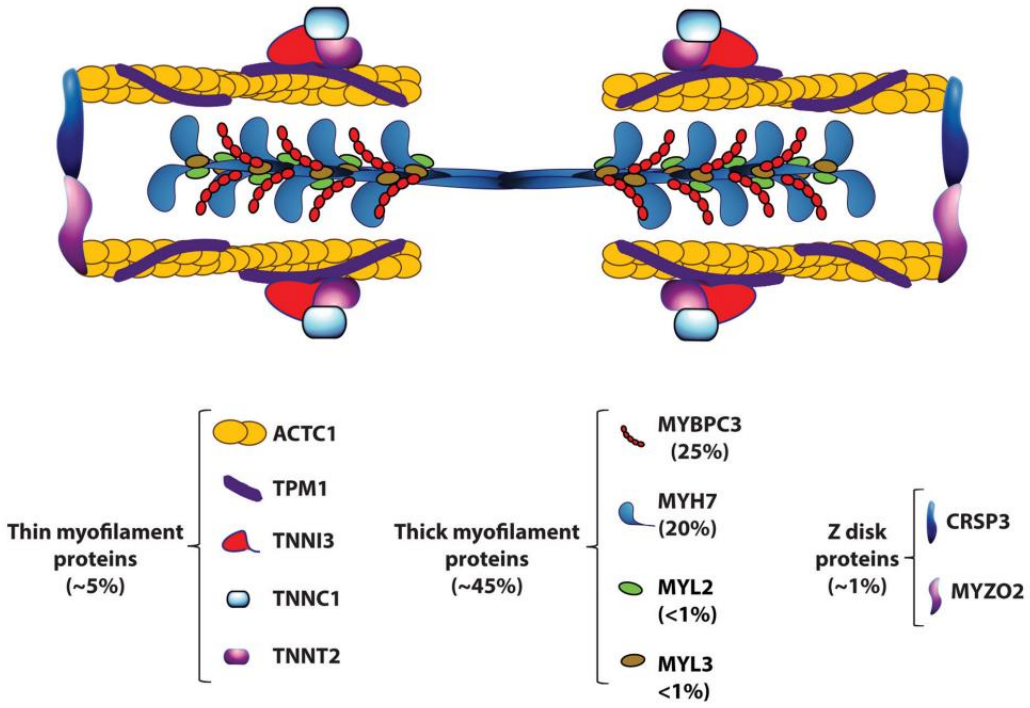
European Heart Journal (2015) **36**, 1367–1370
doi:10.1093/eurheartj/ehv122

CURRENT OPINION

The current role of next-generation DNA sequencing in routine care of patients with hereditary cardiovascular conditions: a viewpoint paper of the European Society of Cardiology working group on myocardial and pericardial diseases and members of the European Society of Human Genetics

Jens Mogensen[1]*, J. Peter van Tintelen[2,3], Siv Fokstuen[4], Perry Elliott[5], Irene M. van Langen[3], Benjamin Meder[6], Pascale Richard[7,8], Petros Syrris[9], Alida L.P. Caforio[10], Yehuda Adler[11], Aris Anastasakis[12], Juan R. Gimeno[13], Karin Klingel[14], Ales Linhart[15], Massimo Imazio[16], Yigal Pinto[17], Ruth Newbery[18], Joerg Schmidtke[19], and Philippe Charron[8,20]

HCM – genetic disease of the sarcomere

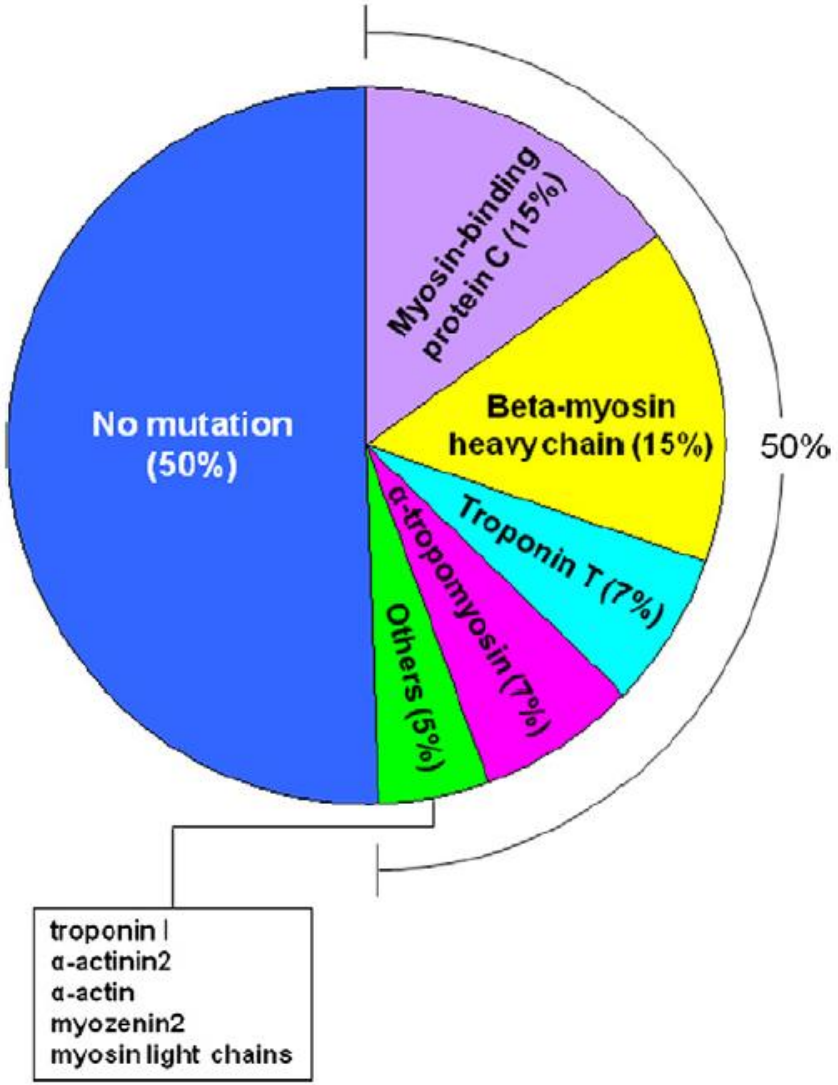


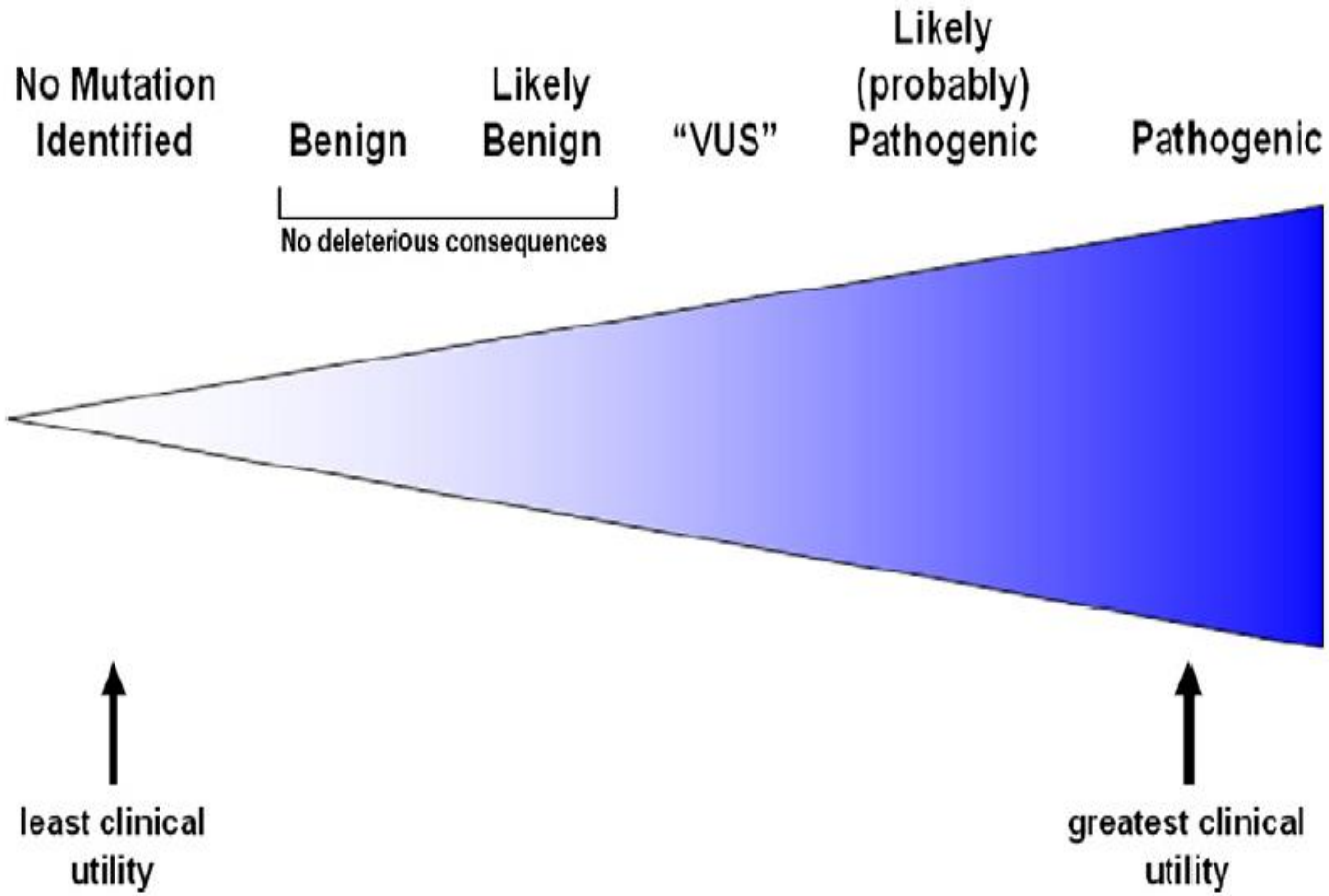
A. Established Causal Gene HCM (Large families)				
Gene	**Protein**	**Function**	**Tolerance to variation**	
			Missense (Z score)	**LoF (pLI)**
MYH7	β-Myosin heavy chain	ATPase activity, Force generation	6.54	0.00
MYBPC3	Myosin binding protein-C	Cardiac contraction	0.69	0.00
TNNT2	Cardiac troponin T	Regulator of acto-myosin interaction	1.54	0.01
TNNI3	Cardiac troponin I	Inhibitor of acto-myosin interaction	1.88	0.17
TPM1	α-tropomyosin	Places the troponin complex on cardiac actin	3.42	0.80
ACTC1	Cardiac α-actin	Acto-myosin interaction	5.25	0.95
MYL2	Regulatory myosin light chain	Myosin heavy chain 7 binding protein	0.86	0.02
MYL3	Essential myosin light chain	Myosin heavy chain 7 binding protein	0.75	0.89
CSRP3	Cysteine and glycine-rich protein 3	Muscle LIM protein (MLP), a Z disk protein	-0.66	0.00

B. Likely causal genes for HCM (small families)				
Gene	**Protein**	**Function**	**Tolerance to variation**	
			Missense (Z score)	**LoF (pLI)**
FHL1	Four-and-a-half LIM domains 1	Muscle development and hypertrophy	1.29	0.92
MYOZ2	Myozenin 2 (calsarcin 1)	Z disk protein	0.03	0.02
PLN	Phospholamban	Regulator of sarcoplasmic reticulum calcium	0.57	0.11
TCAP	Tcap (Telethonin)	Titin capping protein	0.45	0.08
TRIM63	Muscle ring finger protein 1	E3 ligase of proteasome ubiquitin system	0.02	0.00
TTN	Titin	Sarcomere function	−5.48	0.00

Marian and Braunwald Circ Res. 2017 September 15; 121(7): 749–770.

Is gene sequencing the ultimate solution?



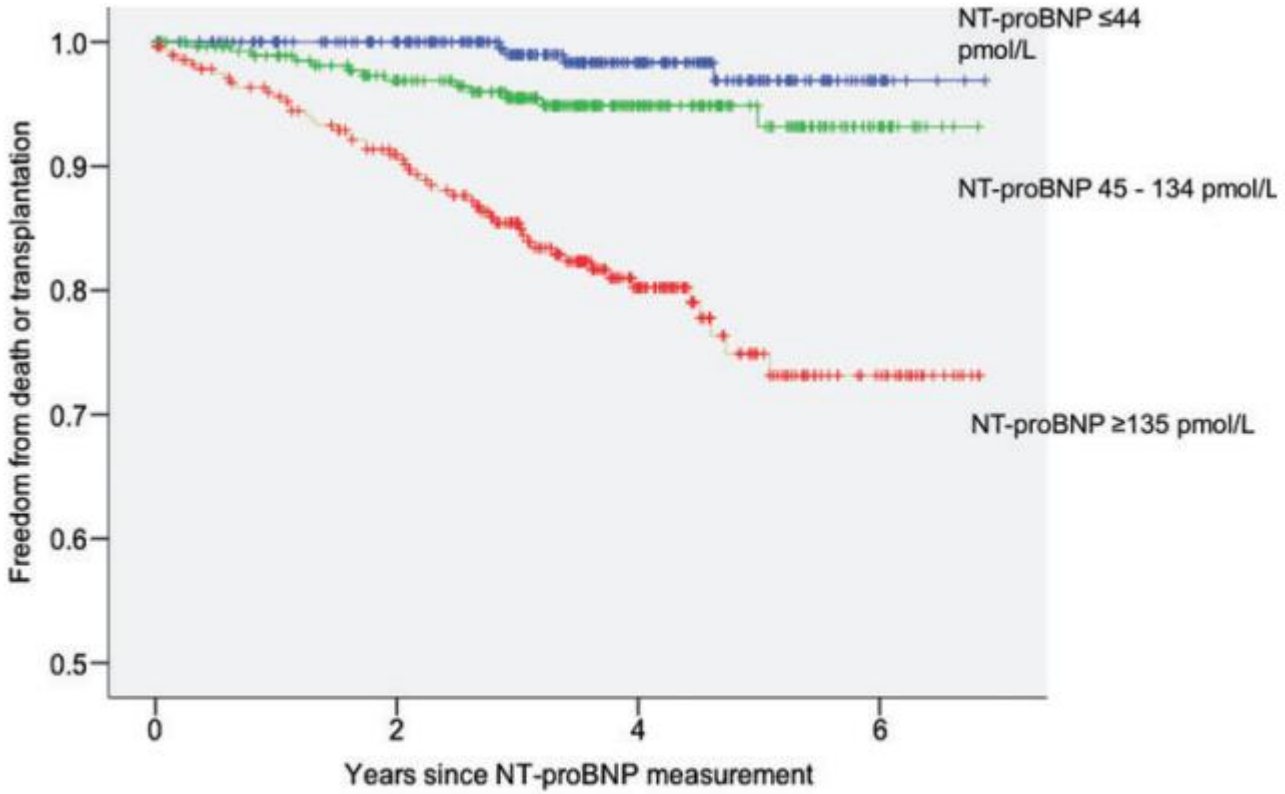


Maron B. et al. J Am Coll Cardiol 2012;60:705–15

STEP 5: RISK ASSESSMENT

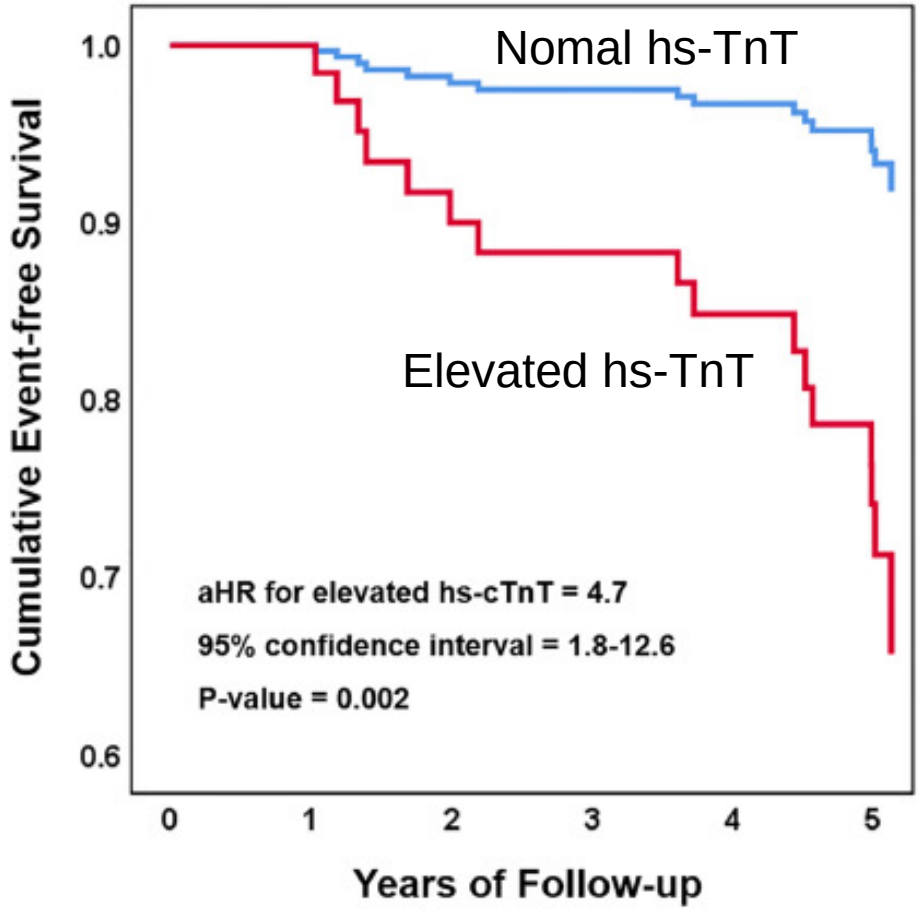
Prognostic implications of NT-proBNP and hs-Tn

847 patients (53+15 years; 67% male) with HCM (28% with LVOTO≥30 mmHg at rest) followed for 3.5 years



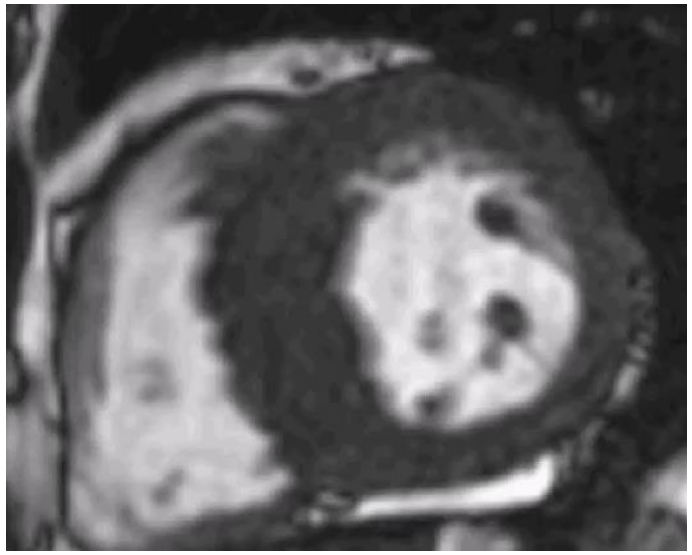
No. at risk				
NT-proBNP ≤44 pmol/L	284	238	106	11
NT-proBNP 45 - 134 pmol/L	281	229	96	16
NT-proBNP ≥135 pmol/L	282	225	100	21

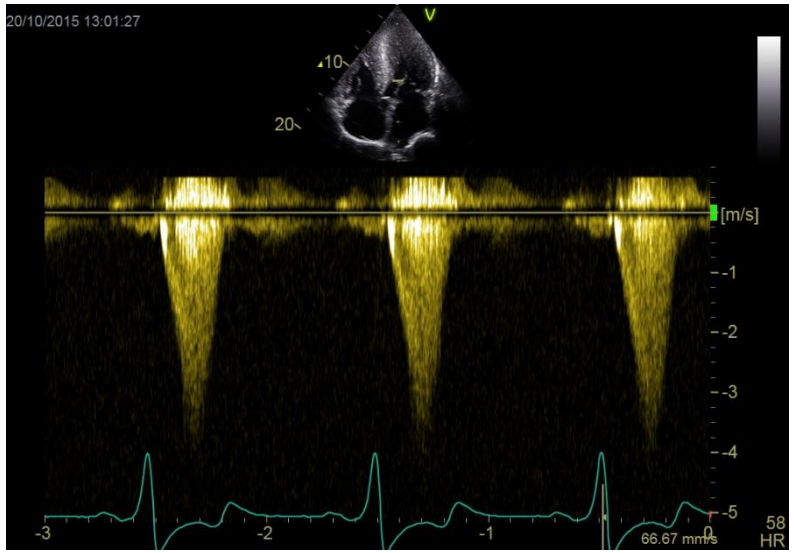
5-year follow-up cohort study of 135 HC patients
↑ hs-cTnT was present in 33 of 135 (24%) HC patients.

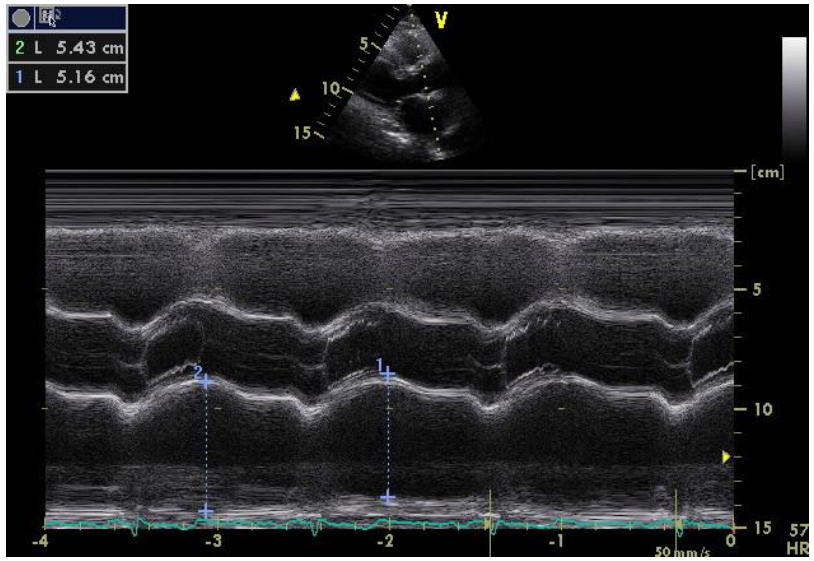


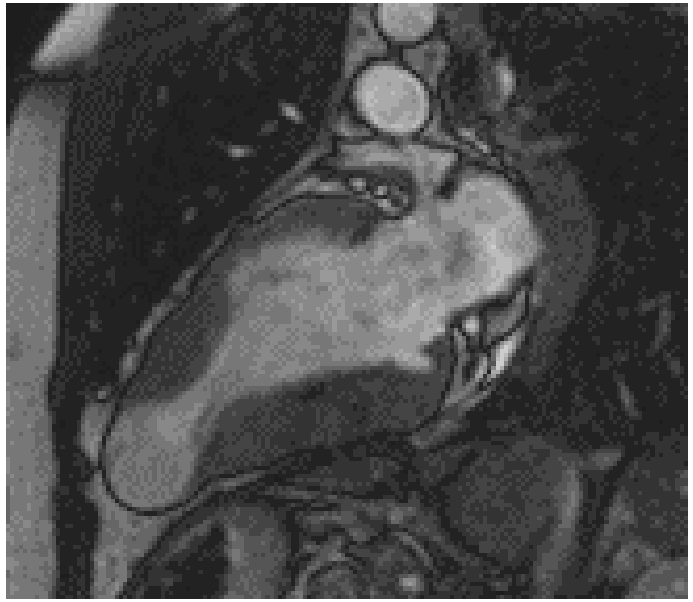
Coats C. et al. European Heart Journal (2013) 34, 2529–2537
Gommans FDH et al. JACC 2021;152:120-124

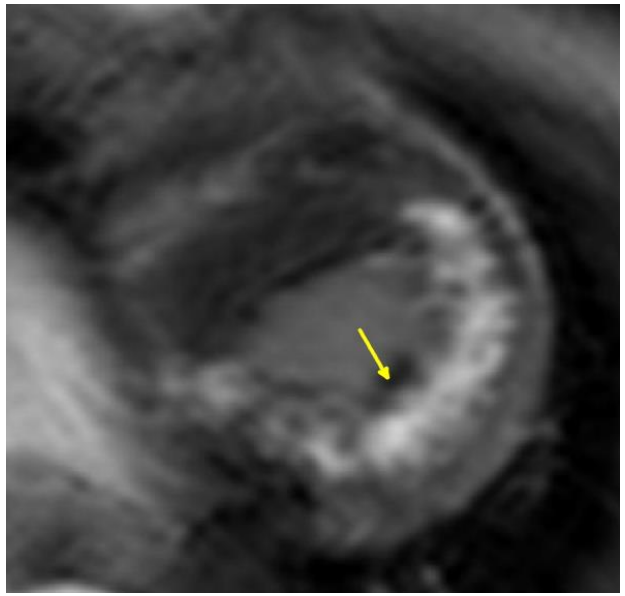
Prognostic implications of imaging

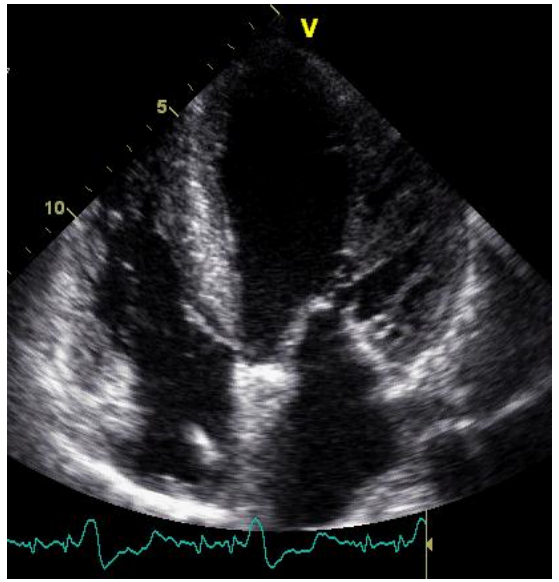






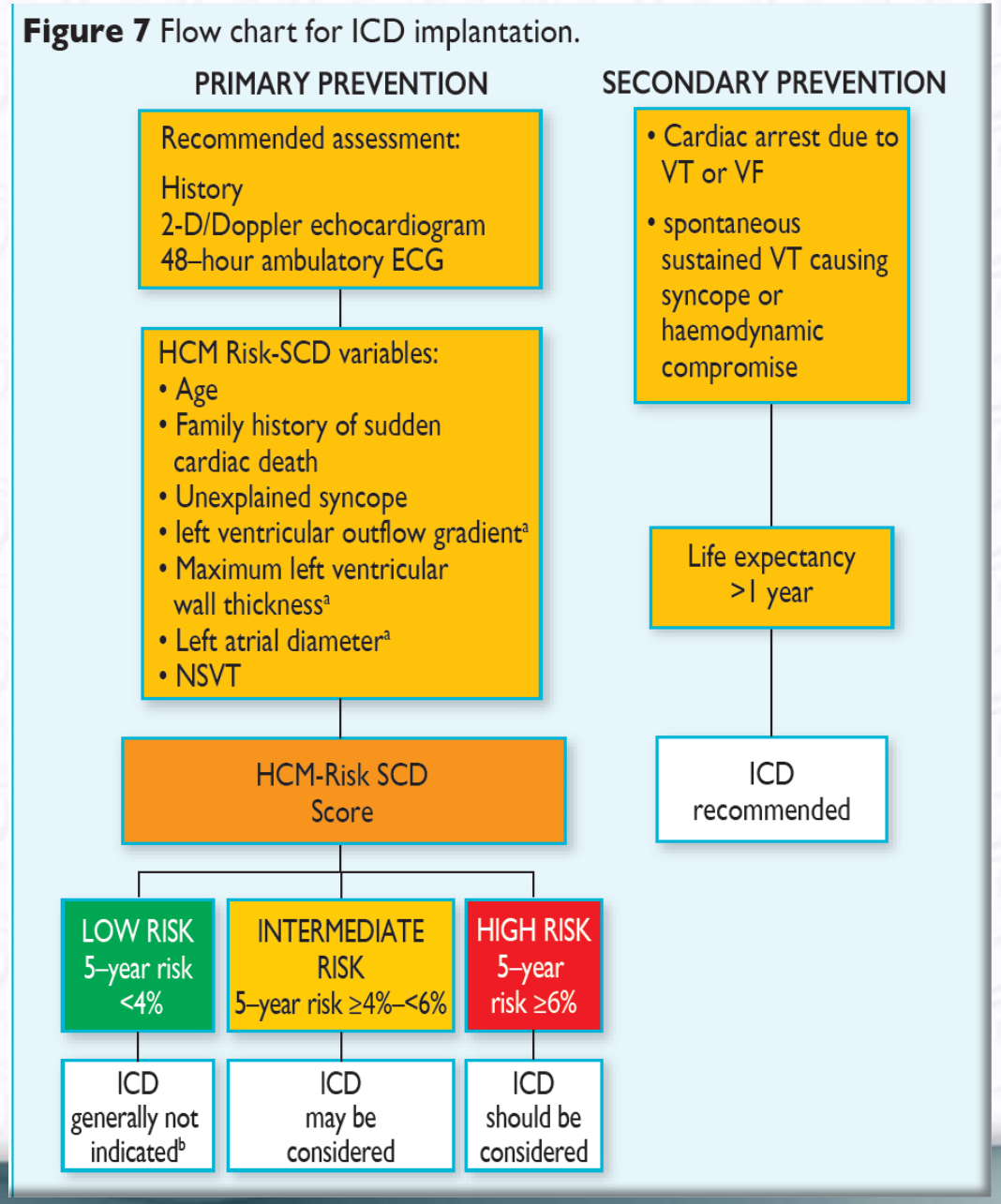






Imaging: General University Hospital Prague, CZ

2020 AHA/ACC Guideline for Diagnosis and Treatment of patients with HCM



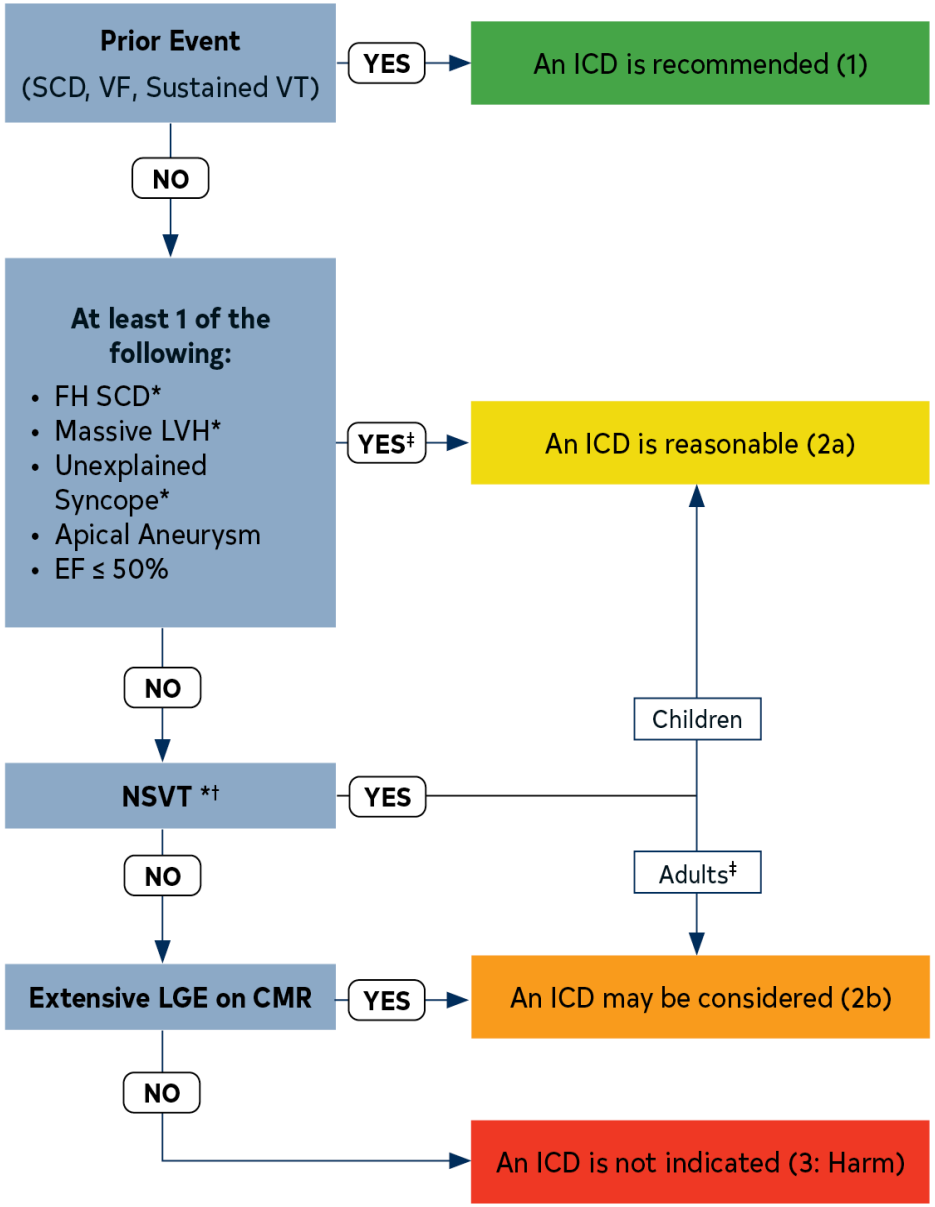
Prevention of Sudden Cardiac Death

Recommendations for ICD in each risk category take into account not only the absolute statistical risk, but also the age and general health of the patient, socio-economic factors and the psychological impact of therapy.

European Heart Journal (2014):doi:10.1093/eurheartj/ehu284

SCD stratification

Family history of sudden death from HCM	Sudden death judged definitively or likely attributable to HCM in ≥1 first-degree or close relatives who are ≤50 years of age. Close relatives would generally be second-degree relatives; however, multiple SCDs in tertiary relatives should also be considered relevant.
Massive LVH	Wall thickness ≥30 mm in any segment within the chamber by echocardiography or CMR imaging; consideration for this morphologic marker is also given to borderline values of ≥28 mm in individual patients at the discretion of the treating cardiologist. For pediatric patients with HCM, an absolute or z-score threshold for wall thickness has not been established; however, a maximal wall that corresponds to a z-score ≥20 (and >10 in conjunction with other risk factors) appears reasonable.
Unexplained syncope	≥1 Unexplained episodes involving acute transient loss of consciousness, judged by history unlikely to be of neurocardiogenic (vasovagal) etiology, nor attributable to LVOTO, and especially when occurring within 6 months of evaluation (events beyond 5 years in the past do not appear to have relevance).
HCM with LV systolic dysfunction	Systolic dysfunction with EF <50% by echocardiography or CMR imaging.
LV apical aneurysm	Apical aneurysm defined as a discrete thin-walled dyskinetic or akinetic segment of the most distal portion of the LV chamber; independent of size.
Extensive LGE on CMR imaging	Diffuse and extensive LGE, representing fibrosis, either quantified or estimated by visual inspection, comprising ≥15% of LV mass (extent of LGE conferring risk has not been established in children).
NSVT on ambulatory monitor	It would seem most appropriate to place greater weight on NSVT as a risk marker when runs are frequent (≥3), longer (≥10 beats), and faster (≥200 bpm) occurring usually over 24 to 48 hours of monitoring. For pediatric patients, a VT rate that exceeds the baseline sinus rate by >20% is considered significant.



2020 AHA/ACC Guideline for Diagnosis and Treatment of patients with HCM

Patient´s trajectory in cardiology practice

Symptoms
- Heart failure
- Arrhythmias
- Syncope
- Sudden death

Asymptomatic
- Screening (ECG, ECHO)

HCM diagnosis in a relative

Step 1: Confirm hypertrophy
- **ECG**
- **Echo**
- **CMRI**

Step 2: Assess LVOTO

Step 3: Differential diagnosis
- **Clinical tableau**
- **Laboratory testing**
- **Imaging**

Step 4: Genetic testing
- **Cascade family testing**

Step 5: Risk assessment

Author´s own opinion